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An investigation of the characteristics of people with Subjective Cognitive Decline and the effects of interventions on cognitive and psychological variables

An investigation of the characteristics of people with Subjective Cognitive Decline and the effects of interventions on cognitive and psychological variables

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Abstract

Current findings suggest that neurodegeneration might start years before a clinical diagnosis of dementia can be made. People at this stage might experience a subjective worsening of their memory, a condition known as Subjective Cognitive Decline (SCD). However, SCD is also a common symptom that might be related to other factors like depression or anxiety. Today, there are no interventions available for people with SCD. The aim of this study was to describe participants with SCD and a smaller sample of people with Functional Cognitive Disorder (FCD) and test the effectiveness of two interventions in people with SCD. Moreover, it investigated the role of genetics in SCD and explored the relation between SCD and Health Anxiety.

It was found that people with SCD score lower than average on the Rey-Auditory Verbal Learning test and people with FCD are more likely to fail a performance validity test. Moreover, SCD participants who are also ApoE4 carriers were more likely to be slower on the working memory task and reported higher levels of stress and depression. In addition to that, participants who were less anxious about their health, were more likely to be aware of their thoughts and feelings. Lastly, this study showed that Mindfulness meditation helped people with SCD to improve their well-being.

These findings constitute a starting point for further understanding SCD and identifying people at a higher risk of dementia. Some of the analyses were exploratory and they constitute a starting point for shaping new hypotheses.

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Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Chapter 1 Introduction

Memory is what shapes all individuals and allows them to exist in time. Without memory, people would not be able to recall the past, or experience the present. Because of its importance, it has been the most popular topic in the field of neuroscience. Even though memory declines with age, in some cases horrible conditions, like Alzheimer's disease (AD) might speed this process up. Today, it remains extremely challenging to identify such conditions at the earliest stage possible and prevent them from progressing. This thesis focuses on Subjective Cognitive Decline (SCD), a condition that has been suggested to be prodromal to AD (Jessen et al., 2010).

1.1 Background

1.1.1 Alzheimer's Disease

Dementia is an umbrella term for conditions that lead to memory loss and decline in other cognitive domains, severe enough to affect everyday living (C. R. Jack, 2012). Alzheimer's disease (AD) is the most common type of dementia and its main characteristic is memory loss. Other AD symptoms include problems with orientation and language, problems with solving tasks and planning, as well as personality and mood changes (C. R. Jack, 2012). When AD was first described more than 100 years ago, it was thought to be an uncommon condition. On the contrary, nowadays it constitutes a major problem for public health. Even though it is a disease and not part of normal ageing, the risk of AD increases as people are getting older (C. R. Jack, 2012). There are around 46.8 million people diagnosed with dementia worldwide and by 2050, this number is expected to reach 131.5 million (Pham et al., 2010). Specifically, in the UK it is estimated that 856.700 people have dementia and around 94% of them are equal or over the age of 65 (Association-of Alzheimer's Disease, 2015), making it the fifth most common cause of death in people over 65 years of age (Heron, 2016).

Evidence from longitudinal studies in the past 20 years have suggested that AD symptoms are insidious and consequently, it is very hard to clearly define its onset (C. R. Jack, 2012). A condition known as Mild Cognitive Impairment (MCI) describes the transitional stage between normal cognition and a clinical diagnosis of dementia (Petersen et al., 2009). MCI constitutes a risk factor for AD development and the rate of MCI patients who convert to AD is around 12% each year, in contrast to the rate for cognitively healthy elderly individuals that is 1%-2% (Petersen, Waring, Smith, Ivnik, & Kokmen, 1997).

The cause of AD is unknown, and the lack of cure makes it one of the most dreaded diseases. All current treatments are targeting the symptoms and they are offered when it is probably quite late in the disease

progression (Hampel et al., 2005). For all these reasons the research interest has focused to early detection of AD, when interventions can be most effective. This thesis discusses SCD and the effectiveness of interventions.

1.1.2 Subjective Cognitive Decline

Prior research has suggested that neurobiological changes may start decades before dementia can be clinically diagnosed (C. R. Jack et al., 2010). In these early stages, people might experience a subjective worsening of cognitive abilities, a condition known as Subjective Cognitive Decline (SCD). As mentioned earlier, it has been suggested that SCD could be a risk factor for AD as it reflects the late stages of pre-symptomatic AD before a diagnosis of MCI can be made (Jessen et al., 2014), (Figure 1.1).

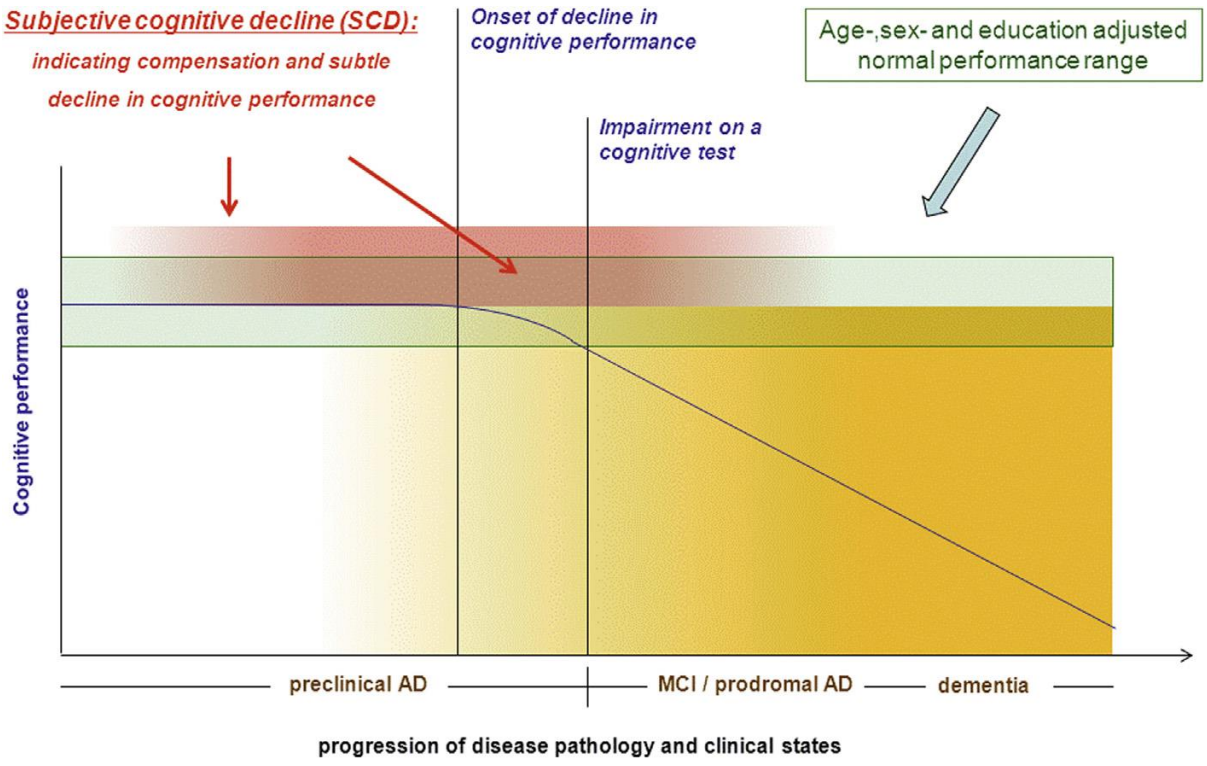

Figure 1.1 This figure details cognitive decline in relation to the progression of Alzheimer's disease (AD) pathology (Jessen et al., 2014)

Unfortunately, SCD is not very specific and the absence of a uniformly accepted set of criteria makes it hard for specialists to diagnose it. A step forward to addressing the concept of SCD was taken in

October 2012 with the formulation of the Subjective Cognitive Decline Initiative (SCD-I). This group of researchers published a manuscript to include a broad definition of SCD and a coding system for its common features, in order to make it easier for other researchers to address the issue (Jessen et al., 2014). According to this framework (Jessen et al., 2014) SCD refers to a subjectively experienced decline of cognitive capacities compared to previous normal status and is not related to an acute event. This condition is also independent of somebody's scores on cognitive testing (Jessen et al., 2014).

The set of criteria proposed by the SCD-I have been described within the AD framework. However, the same characterisation could have been useful within the clinical setting. In more detail, such criteria have been developed around two major axes (Jessen et al., 2020). The first one refers to the subjective experience of memory decline, in comparison with a previously normal cognition. This implies that the individual is experiencing a decline in their cognitive function, but this is not necessarily something that can be observed by people around them. The second criterion requires that the individual performs within the normal limits on standardised cognitive testing and shows no impairment of cognitive function (Jessen et al., 2020).

At this point, it is interesting to mention that SCD has not been included in the Diagnostic and Statistical Manual of Mental Disorders-5 or the International Classification of Diseases-11, as a diagnostic category.

A recent paper found that people with SCD showed greater level of depression, anxiety and neuroticism when compared to people without SCD. It also reported that unlike the non-SCD group, SCD participants' scores on the self-reported measures were correlated with their objectively measured performance on memory test (visual and verbal memory) and depression, anxiety and quality of life questionnaires (Jenkins, Tree, Thornton, & Tales, 2019). These findings highlight the need for a personalised approach to SCD, instead of group level comparisons based only on the psychometric test outcomes.

One meta-analysis that has included longitudinal epidemiological studies of cognitively intact people with SCD, found that 14% of them went on to develop dementia, whereas 27% developed MCI (Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014). On the contrary, there are others studies that have reported no association between SCD and cognitive decline (Hessen et al., 2017). Some other long-term prospective studies however, that included people with SCD who later on declined to dementia, hypothesised that SCD can occur even 10 years before an official diagnosis of dementia is made (Amieva et al., 2008; Verlinden et al., 2016). Even though SCD is not always linked to progressive cognitive decline, it is still an important condition that needs to be further defined as it constitutes a possibly detrimental threat to some individuals' cognition and quality of life.

Looking further into the set of criteria proposed by the SCD-I group, the authors have also described the "SCD-plus" features. These are SCD characteristics that suggest a specific risk of cognitive

deterioration (Jessen et al., 2014). The first SCD-plus characteristic is the subjective experience of memory decline, regardless of function in other cognitive domains. The second feature is the onset of SCD to be in the past 5 years. According to longitudinal studies (Amieva et al., 2008; Verlinden et al., 2016), SCD might occur around a decade before a diagnosis of dementia is made. Considering that SCD might progress to MCI before dementia, an SCD onset that exceeds the 5 years, is less likely to predict future dementia, than an onset in the past 5 years.

The third SCD-plus feature refers to the onset of SCD at 60 years of age or older (Jessen et al., 2014). This is easily explained if we consider that people younger than this age are less likely to have an underlying medical condition causing future dementia. Consequently, people who are younger than 60 years old are more likely to have SCD due to a potentially reversible condition, compared to people older than 60 years of age. The fourth feature of SCD plus is the expression of SCD-related worries. Evidence suggests that people who are concerned about decline in cognition are at higher risk of developing future dementia (Jessen et al., 2010; Verfaillie et al., 2019). Lastly, validation of cognitive decline by an informant constitutes the fifth feature of SCD-plus. Evidence suggests that if an observer confirms that a person with SCD is cognitively deteriorating, then there are higher chances that they will develop future cognitive decline (Valech et al., 2015).

Some very hopeful steps in the characterisation of SCD have been recently suggested by Jessen and colleagues (2020). The authors propose that, in order to evaluate the concern expressed by people with SCD, we must acquire some additional information. This information includes the onset of the cognitive deterioration, the cognitive functions affected, whether the concerns are specific and whether there are any links between the concerns and any medical conditions or the use of alcohol or medication (Jessen et al., 2020).

As discussed previously, even though SCD might serve as a pre-clinical indicator of AD (Jessen et al., 2014), it also constitutes a common and heterogeneous condition which has not yet been fully described (Tales et al., 2015b). Some causes of SCD include normal ageing, other neurological or medical disorders, the effects of medication or substance use, psychiatric disorders and other psychological factors including health anxiety and depression (Slavin et al., 2010).

Besides being common, SCD can also be very distressing especially due to the fear of developing dementia. However, the evidence regarding the effectiveness of treatments for this condition is limited (Stewart, 2012). Recent studies that focused on interventions for SCD, have evaluated methods such as cognitive skills training (Power, Kirwan, & Palmer, 2011) and a nutritional intervention (Richter, Herzog, Eyal, & Cohen, 2011). In one randomised controlled trial, a group of older women who had reported SCD without any evidence of objective impairment, received information regarding cognitive ageing (aiming at compensatory behaviour) as an intervention. Compared to the controls, these people showed less negative emotional reactions towards their cognitive function (Hoogenhout, de Groot, van

der Elst, & Jolles, 2012). Other projects have reported greater response to such interventions in people who are more physically active (Thiel et al., 2012).

The key difference between SCD and MCI is the fact that although both groups express memory complaints, people who are susceptible to MCI will present objective cognitive impairment. By that, I mean that their scores on cognitive tests will be lower than expected for their age and education.

Lastly, as mentioned above the main problem with SCD is the lack of standardised neuropsychological tools to diagnose it. Consequently, this diverse group requires further investigation in order to uncover whether the symptoms are early indicators of neurodegeneration, indirect manifestation of a psychological condition like depression or health anxiety, or if it is just a benign symptom that could be due to factors like normal ageing.

1.1.3 Subjective Cognitive Decline and Mild Cognitive Impairment

The main characteristic that makes SCD distinct from MCI is the absence of objective cognitive impairment. Sometimes, clinical judgment alone, might lead to a diagnostic overlap of these two conditions and for this reason, many clinicians use either short or longer psychometric assessments (Albert et al., 2011). However, the diagnostic accuracy of short screening tests like the Montreal Cognitive Assessment or the Mini-Mental State examination might be limited (Tsoi et al., 2017). Instead, the use of more comprehensive and extended neuropsychological test batteries that are adjusted to age, sex and education, along with a universally accepted cut-off point would be the key to differentiating SCD from MCI.

Today, people with MCI can be referred to a memory clinic by their General Practitioner (GP) for further assessment and a formal diagnosis. Similarly, individuals with SCD can also receive a formal diagnosis from memory services but not everyone who is experiencing a change in their cognitive function seeks medical assistance (Hurt, Burns, Brown, & Barrowclough, 2012). It is really difficult to know the size of this group but, an interesting paper has reported that the main difference between help-seekers and non-seekers in an SCD group, was not objective impairment but rather the beliefs about memory. Moreover, individuals who had previously sought medical attention were more likely to have had a family member with dementia (Hurt et al., 2012).

1.1.4 Functional Cognitive Disorder

Forgetting a telephone number or a task, constitutes part of daily living. In some cases, increasing forgetfulness might lead an individual to seek medical help. Some of these individuals might feel reassured after receiving the “all-clear” following a neuropsychological assessment ,while others might

present with cognitive changes that occur due to normal ageing, or have underlying psychological conditions (Deary et al., 2009). People who are reporting psychological difficulties and also experience subjective cognitive changes that cannot be medically explained, are characterised by Functional Cognitive Disorder (FCD) (Metternich, Schmidtke, & Hull, 2009).

It has been proposed that FCD patients constitute a subgroup of people with SCD where intellectual symptoms are significantly linked to psychological factors which might not always be evident. According to estimates provided by prior research, 6-13% of individuals presenting with memory concerns have a psychological or functional origin to their complaints (Metternich, Schmidtke, Harter, Dykierek, & Hull, 2010). Despite the fact that FCD seems to be a common condition (one third of patients aged <60 years received the final diagnosis of FCD in a recent audit of the North Bristol Trust ReMemBr cognitive clinic database), it is yet fairly under-studied (Pennington, Newson, Hayre, & Coulthard, 2015).

People with FCD normally report stressful life situations like the loss of a beloved person, or events that relate to chronic stress. After noticing their memory lapses, these people experience fear and anger which in turn, leads to even higher levels of stress. Ultimately, stress triggers more memory failures and the sufferers end up in a vicious circle that could be best described by a model similar to the one of somatoform disorders (Metternich et al., 2009).

The core clinical features of this condition include at least one cognitive symptom that causes distress and/or impairment in daily functioning. Another FCD characteristic is the inconsistency between neuropsychological test results and self-reported symptoms. Such symptoms usually do not show any objective progression over time and are not possible to be explained by another general medical, neurodegenerative, neurological or mental condition. However, FCD should not be diagnosed until other causes of cognitive decline are excluded, such as early neurodegeneration. Other conditions that FCD should be distinguished from are dissociative amnesia, anxiety disorder and dementia phobia condition (Pennington, Newson, et al., 2015).

The most important thing for clinicians to keep in mind when diagnosing FCD, is the difference between objectively measured cognitive functioning and self-reported experience. This inconsistency is evident when comparing for example, an individuals' complaint of inability to recall newly obtained information while, still performing within the normal limits on a cognitive test (Pennington, Ball, & Swirski, 2019).

As mentioned above, FCD is a recently studied clinical entity and the cause of it might be related to psychological variables. It exists within a spectrum that ranges from SCD to dementia (Pennington et al., 2019). FCD is distinct from SCD as it manifests more severe symptoms and a discrepancy between the subjective experience and the objective observation of functioning. People with FCD also tend to be more resistant to reassurance that their cognition is unimpaired. Moreover, another issue with these

two cognitive diagnoses is that SCD seems to be quite common whereas, the prevalence of FCD is still being examined (Pennington et al., 2019). However, the true prevalence of SCD might not be yet properly estimated due to the lack of a universal set of criteria and its variable terminology.

It seems that FCD can be compared to SCD regarding the expression of memory concerns. Nevertheless, I would argue that in the case of FCD there is probably a clearer underlying psychological mechanism. This mechanism is similar to the somatoform model (Berrios & Hodges, 2000; Schmidtke, 1995) and describes how psysiological or psychological stress triggers concentration and memory problems (Metternich et al., 2009). What makes this condition even more interesting is the hypothesis that psychiatric symptoms might sometimes be indicators of future neurodegeneration (Stella et al., 2014). Therefore, in order to make a correct diagnosis, clinicians should examine how severe is the symptomatology and the discrepancy between subjective and objective cognitive function. Additionally, they should take into account any underlying psychological factors and of course look for any metabolic or neurodegenerative cause of the decline. Lastly, it is important to remember that people with FCD are not immune from future cognitive decline (Pennington et al., 2019).

1.2 Bio-Psycho-Social Approaches to SCD and FCD

The aim of this section is to provide a more in-depth understanding of the Biological, Psychological and Social approaches to SCD and FCD.

Unfortunately, FCD is infrequently discussed and there are not currently any studies investigating its biological basis. Considering its relationship to SCD and memory concerns, it is likely that it would follow a similar pattern to SCD genetic basis but at this time there is not enough evidence to support such hypothesis. Consequently, the next section discussing genetic factors is focussing on SCD.

1.2.1 Genetics of SCD

The Apolipoprotein E (ApoE) gene has been linked to faster cognitive decline and poorer memory performance in AD patients (Cosentino et al., 2008). There are 3 common versions (alleles) of the gene E2, E3 and E4 and everyone inherits two ApoE genes, one from each parent. Therefore, people will usually have one of the following six combinations or "genotypes": E2/E2 (1%), E2/E3 (11%), E2/E4 (2%), E3/E3 (61%), E3/E4 (23%), and E4/E4 (2%) with the figures in the brackets indicating approximately what proportion of the UK population have that gene. Although 40-65% of AD patients have at least one copy of the E4 allele, ApoE4 is not a determinant of the disease and at least a third of patients with AD are ApoE4negative and some ApoE4 homozygotes never develop the disease. Yet those with two E4 alleles have up to 20 times the risk of developing AD. There is also evidence that the ApoE2 allele may serve a protective role in AD.

ApoE4 represents the biggest genetic risk factor not only for AD, but also for MCI (Kryscio, Schmitt, Salazar, Mendiondo, & Markesbery, 2006). There is growing interest around the impact of the ApoE gene on the SCD population (Moreno-Grau et al., 2018). Earlier evidence suggests that both subjective memory complaints and ApoE4 allele carriage might have an additive effect on future cognitive impairment (Dik et al., 2001). Moreover, a meta-analysis showed that having the ApoE4 gene is linked to AD progression in individuals with SCD and is also associated with the possibility of having SCD, in cognitively intact participants (Moreno-Grau & Ruiz, 2016). One systematic review has reported that in the SCD population, being an ApoE4 carrier is an additional risk factor for future cognitive deterioration (Ali, Smart, & Gawryluk, 2018). Lastly, another study suggested that ApoE4 and SCD had a positive interaction effect on the risk of developing MCI 5 years later but interestingly enough, this effect was only observed in women (Muller-Gerards et al., 2019).

Despite the fact that an over-representation of the ApoE4 allele has been reported in individuals with SCD (Small, Perera, DeLaPaz, Mayeux, & Stern, 1999), its effect on these people's cognitive performance is yet to be explored.

As the role of the ApoE gene and SCD in the field of dementia research is growing, one of this thesis's aims is to investigate whether ApoE4 carriers and ApoE2 carriers would have different characteristics and performance (cognitive/psychological) compared to non-carriers, in people with memory complaints.

1.2.2 Health anxiety

An important notion in this study is the term "Health anxiety". Health Anxiety refers to a broad diagnostic construct which encloses constant worries about illness, varying from mild to severe levels (American Psychiatric Association, 1994). Health Anxiety also involves excessive fear due to a perceived health problem (Jonathan S. Abramowitz & Braddock, 2008). Usually, people with high levels of Health Anxiety might translate bodily sensations or health-related information into symptoms of a threatening illness. Such thoughts will eventually lead to feelings of distress (Asmundson, Abramowitz, Richter, & Whedon, 2010).

It has been proposed that Health Anxiety occurs in a continuum (Longley et al., 2010) ranging from mild health-related anxiety, to pathological anxiety which could be linked to impaired functioning and discomfort (Asmundson et al., 2010).

The most recent approach to this condition comes from the cognitive-behavioural theories (Salkovskis & Salkovskis, 1996; Warwick & Salkovskis, 1990) according to which, individuals experience Health Anxiety when they tend to misinterpret health-related information and physical sensations as indicators of a serious physical illness. These dysfunctional beliefs around health are maintained by memory

biases (H. D. Brown, Kosslyn, Delamater, Fama, & Barsky, 1999) and different "safety" behaviours that aim to reduce the distressing anxiety symptoms (J. S. Abramowitz & Moore, 2007). Some of these behaviours include seeking reassurance (from family, friends and health professionals), avoiding what they would consider to be a risky activity (even if it is not, like exercising for example) and constant checking (frequently examining the body for any illness symptoms). Evidence suggests that these behaviours lead to more dysfunctional beliefs, resulting ultimately into the maintenance of Health Anxiety (Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011).

There is currently no bibliography examining the relationship between Health Anxiety and SCD or FCD. However, it seems that Health Anxiety is of great clinical relevance especially if we consider the patterns of "safety" behaviours. As discussed above, one of these behaviours is the misinterpretation of symptoms and constantly seeking reassurance about the severity of them. Going back to the FCD population it is likely that resistance to medical reassurance in some FCD patients (Pennington et al., 2019) could be related to this Health Anxiety behaviour. For example, someone who is worried about their memory and cognitive function might visit quite often a memory service in order to alleviate the anxious feeling that something could be wrong with their cognition, even after performing well on a cognitive assessment and their everyday tasks.

Furthermore, increased worrying about health reminds us of the memory concerns and a potential fear of developing dementia that is nested in the SCD population. In the absence of any objective cognitive impairment, such fears could be associated with memory biases and generally higher levels of Health Anxiety.

In this thesis, I will investigate whether high or low Health Anxiety is associated with cognitive function and other psychological factors, in SCD population.

1.2.3 Interventions

At present, there is little to offer to people with SCD in terms of support or treatment because services are focused on people who have a diagnosis of dementia. It is likely that effective support and appropriate intervention for SCD patients could provide significant benefits regarding maximising cognitive, emotional and physical health.

For example, Grossman, Niemann, Schmidt, and Walach (2004) found that mindfulness meditation courses were cost-effective and produced measurable improvements in health and for a wide range of health conditions. Additionally, a 2-year follow-up study of people diagnosed with MCI in a population-based sample (Sachdev, Lipnicki, Crawford, Reppermund, Kochan, Trollor, Wen, Draper, Slavin, Kang, Lux, Mather, Brodaty, & Team, 2013), reported that factors such as engagement in mentally stimulating activities and better control of blood pressure could facilitate reversion to normal cognition.

Therefore, an early intervention designed to target lifestyle and other relevant factors could be a cost-effective preventative measure against further cognitive decline in people expressing cognitive complaints.

In this study, participants are offered two different interventions, one that is already commercially available and a second one that is created for the purposes of this project. The purpose is to evaluate them by examining their effect on cognitive and psychological outcome measures. Each intervention is described below in turn.

1.2.3.1 Mindfulness

Mindfulness meditation is a mental state achieved by focusing one's awareness on the present moment experience, while calmly accepting feelings, thoughts and bodily sensations (Detert, 2015). It has been suggested that practicing mindfulness can maximise physical as well as emotional and cognitive health. There is evidence that mindfulness practice can be an effective treatment for functional symptoms (Lakhan & Schofield, 2013). For the purposes of this study I offered those who had been assigned to the meditation intervention, a 4-week online course of mindfulness meditation.

The course is called "Be Mindful Online" (for more information see www.bemindfulonline.com) and has been developed to cover the core elements of Mindfulness-Based Cognitive Therapy (MBCT) and Mindfulness-Based Stress Reduction (MBSR). The effectiveness of this course has been described by a study at Oxford University published in BMJ open (A. Krusche, E. Cyhlarova, S. King, & J. M. G. Williams, 2012). The reported average outcomes for people who completed the course, indicated that they had 58% less anxiety, 57% lower depression levels and 40% less stress. It is a 4-week programme with spoken instructions in order to become aware of experiences and not judge themselves when attention goes elsewhere. For example, in the first week of the course the "body scan" practice involves moving the focus of attention systematically through all parts of the body over a 40-minute period, focussing on sensations. Other practices include simple physical stretches with mindful awareness of sensations, and sitting with awareness of breathing sensations, sounds, thoughts and feelings. During the course, there is emphasis on observation of thoughts and the effects of thoughts on mood, supplemented by experiential exercises and psychoeducation. I expected that after the end of the course, participants would continue daily practice to maintain the benefits.

1.2.3.2 Lifestyle intervention

According to examinations within the Caerphilly study (Elwood et al., 1999b) a person is able to reduce his or her risk of developing dementia by up to 60% by being physically active, socially engaged, avoiding smoking and drinking too much alcohol and eventually, committing to review his or her health.

Furthermore, the FINGER study (T. Ngandu et al., 2015) showed that a multidomain intervention can improve or maintain cognitive functioning and reduce the risk of cognitive decline among at-risk individuals. The most interesting part of this study though, was the fact that, compared to most studies, researchers shifted the focus to presymptomatic and predementia disease stages and at-risk states when intervention can be most effective. Moreover, a different study suggested that complex mental activity acts protectively against cognitive decline and dementia (Valenzuela & Sachdev, 2006).

Drawing from the evidence provided in current scientific literature, I designed a 4-week educational programme that presented information relevant for promoting and maintaining optimum cognitive function. The sources included evidence from studies like the FINGER study (Tiia Ngandu et al., 2015), the "Sharp brains: guide to brain fitness" (Fernandez, 2013), the "Hello brain" website (www.hellobrain.eu), and a 6 steps leaflet for reducing dementia risk, produced by Tony Bayer and the Wales Government. This intervention was also inspired from the Transtheoretical Model of Change which encourages positive change (Prochaska, Norcross, & DiClemente, 1994). Just like the mindfulness course, this intervention was delivered in weekly instalments, with participants monitoring their compliance with its recommendations, using a diary and a physical activity sheet. Keeping information in this way can also promote and maintain positive change in everyday habits.

The content of this intervention included a description of factors associated with improved outcome for cognitive function and general health. These are lifestyle factors such as exercise, diet, mental stimulation and social engagement, which have been linked to reduced risk of developing dementia and to a slower rate of memory decline in normal ageing (Stern, 2009). In the following section I am describing the four intervention domains in more detail.

1.2.3.2.1 Physical activity

The first week of the course focussed on physical activity. Over the past two decades, there has been increasing focus on the impact of exercise on brain function in older adults and how it can reduce the risk of cognitive decline. In the next paragraphs I will review the evidence that is available.

One study included men and women over the age of 65 who had no memory problems. They were asked to report how many times per week they performed a physical activity, lasting at least 15 minutes. After a follow-up period of approximately 6 years, some of the participants had developed Alzheimer's disease. The results suggested that people, who exercised less than 3 times per week, were at higher risk of developing the disease compared to people who exercised 3 times per week or more (Larson et al., 2006).

A very interesting finding in this project was that the reduction in risk for the disease was even greater for the people who had the lowest level of physical exercise when they started the study. So, the key point is that it is never too late to change.

A different study found that in people between 65 and 79 years of age, physical activity during leisure time at least twice a week was linked with a 52% reduced risk of developing dementia (Rovio et al., 2005).

There are two main types of exercise: aerobic and non-aerobic. Aerobic exercise refers to exercise that increases the heart rate and breathing rate to an optimum level. Non-aerobic exercise refers to exercise where the heart rate is not increased to the same level, such as lifting weights or playing golf. Most human and animal studies on this topic have shown that aerobic exercise is the best exercise for improving memory function.

Based on the evidence so far, aerobic exercise that will raise the heart rate and breathing rate for 15 minutes, at least 3 times per week is recommended to optimise brain health. Therefore, throughout the course participants were asked to perform a brisk walk for 15 minutes, 3 times per week for four weeks.

The brisk walk did not need to be strenuous, but it had to be some sort of exercise and not simply strolling down the street. It was also made clear that they would need the appropriate gear (good walking shoes and probably a raincoat) and of course, warm up and gently stretch before they start, in order to avoid any accidents or injuries. I advised that in case they felt uncomfortable while exercising, they should use their own judgement, stop exercising, and see their GP for advice, in order to clarify that they should by no means push themselves to carry on (if they were feeling unwell) just because they are part of the study.

1.2.3.2.2 Diet

The next week of the course focused on how eating and drinking habits, and related factors such as sleep, can affect brain health. I will review the evidence below.

A number of studies have shown that some dietary choices are better than others when it comes to promoting brain health and delaying the effects of age and dementia (Solfrizzi, Panza, & Capurso, 2003) and just like the heart, the brain benefits from a diet that includes plenty of fruits and vegetables and less saturated fatty acids.

There are two types of fatty acids: saturated and unsaturated. Certain types of unsaturated fatty acids are important for our health. Omega-6 and Omega-3 fatty acids may be especially important for brain health. Omega-3 fatty acids have been shown to have antioxidant properties and they have been shown to have a protective effect against inflammation (Uauy & Dangour, 2006) and the accumulation of a protein called amyloid in rats, which is one of the signs of Alzheimer's disease in the brain (Puskas, Kitajka, Nyakas, Barcelo-Coblijn, & Farkas, 2003).

One way to obtain Omega-6 fatty acids is through vegetable oils, and vegetable oils are fairly common in diets. As for Omega-3 fatty acids, one of the best dietary sources is oily fish such as salmon, tuna

and mackerel. For some people this type of fish may be eaten rarely or not at all, and that may be why many people in Europe and the US are not obtaining optimum levels of Omega-3 fatty acids.

Also, there is evidence that eating fish – and that includes fresh fish, fish sticks, fish cakes, and tuna sandwich fillings – one or more times per week, might protect against Alzheimer's disease and age-related cognitive decline (Morris et al., 2003; Morris, Evans, Tangney, Bienias, & Wilson, 2005). For people with fish allergies and vegans or vegetarians, there are other sources of Omega-3 fatty acids. However, the evidence suggests that Omega-3 supplements on their own do not have a significant impact on cognitive function. It is not yet clear whether there are longer-term effects of Omega-3 supplementation on risk of developing dementia. More research with longer term follow-up is needed (Sydenham, Dangour, & Lim, 2012).

Consequently, it is possible that the benefits of eating fish are not simply due to the Omega-3 fatty acids present in the fish, but they may be related to other elements of fish. Again, more research is needed in this area before firm conclusions can be made.

Another nutritional factor that has been proposed to have positive effects on brain health is antioxidants. Antioxidants are substances that inhibit oxidation and they can delay or prevent some types of cell damage. Besides omega-3 fatty acids, other antioxidants such as beta-carotene, flavonoids, Vitamin C and Vitamin E have been investigated in several studies. The main dietary sources of beta-carotene are carrots, kale, broccoli and spinach. Flavonoids can be obtained through cranberries, green and black tea and pulses such as lentils and beans. Important sources of Vitamin C are citrus fruits, cabbage, broccoli, red peppers and kiwi. Vitamin E can be found in nuts, milk and grains.

Blueberries have also been suggested as a great source of antioxidants that could protect the brain against cognitive decline. The main evidence for their benefits so far comes from animal studies (Shukitt-Hale, 2012) but a recent study with a small number of people with mild cognitive impairment reported that daily supplementation of blueberry juice for 12 weeks improved their memory function (Krikorian et al., 2010). Further research is needed using controlled clinical trials to investigate whether blueberries can help protect against cognitive decline.

The effects of antioxidants on cognitive function and risk of dementia have been investigated in several studies and the results have been inconsistent (Crichton, Bryan, & Murphy, 2013). One long-term prospective study assessed the dietary habits of women aged 70 years and older and concluded that high consumption of vegetables was related to less cognitive decline. Moreover, stronger associations were found with greater consumption of green leafy vegetables, like spinach and romaine lettuce and cruciferous vegetables, such as broccoli and cauliflower (Kang, Ascherio, & Grodstein, 2005). The health benefits of a diet rich in fruits and vegetables is clear, but whether this is due to their antioxidant components remains to be seen.

A type of diet that has recently received a lot of attention because of its protective role against cardiovascular disease, different types of cancer and other illnesses is the "Mediterranean diet". It has also been linked with reduced risk of cognitive decline (Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006). The hallmark of Mediterranean diet is a high consumption of olive oil. Olive oil is a rich source of monounsaturated fatty acids, a type of unsaturated fatty acid (like Omega-3 and Omega-6) which reduces the so-called "bad" cholesterol and raises the "good" cholesterol levels in the bloodstream. The Mediterranean diet also involves high consumption of fruit, vegetables, pulses (such as lentils and beans), whole grains, cereals, and nuts and a moderately high consumption of fish. It is also characterised by a relatively low intake of saturated fats, meats and poultry and a low-to-moderate intake of dairy products. Finally, it often includes a moderate intake of wine during meals (Willett et al., 1995).

Regarding eating foods high in cholesterol and saturated fat, there is consistent evidence from both epidemiologic and clinical studies that these foods are associated with an increased risk of cognitive decline (Kalmijn, Feskens, Launer, & Kromhout, 1997). Examples of such foods include processed meat, like sausages, salami or ham, red meat and other fatty cuts of meat, fried food, high fat dairy foods such as butter and cheese, eggs and coconut and palm oils. Also, foods made with these ingredients will be high in cholesterol and saturated fat, like cakes, biscuits and meat pies.

Also, a diet high in cholesterol and saturated fat is associated with risk of cardiovascular disease which is, in turn, a risk factor for cognitive impairment (Breteler, 2000). In fact, recent evidence has shown that "what is good for the heart is good for the brain", and this is a good maxim to live by when choosing what to eat or drink.

It has been proposed that caffeine intake could protect against the effect of ageing on cognitive decline. A case-control study found that high caffeine intake was associated with a lower risk of developing dementia, or a later onset of dementia in people who already had mild memory problems (Cao et al., 2012). Moreover, a large prospective study showed that women with higher consumption of caffeine (over three cups of coffee or tea daily) had greater protection against cognitive decline compared to women with lower consumption, who drank two to three cups daily (Ritchie et al., 2007).

Coffee is a rich source of caffeine, and a population study showed that consumption of coffee (at least 3 cups a day) is linked to less cognitive decline in older men (van Gelder et al., 2007). However, more long-term research is required, and definite conclusions cannot be made about caffeine as it is possible that the effects of coffee and tea on memory and thinking are different.

There has been more research on the relationship between alcohol consumption and brain health. There is little doubt that excessive drinking over a long period can cause damage to the brain and it has been linked to an increased risk of developing dementia (Saunders et al., 1991). On the other hand, one study

showed that light-to-moderate alcohol intake was related to a lower risk of dementia in people aged 55 and older (Ruitenberg et al., 2002).

A study published in 2006 included people aged 60 and over who were asked about their drinking habits and were followed up for two years. Researchers found that people who drank a light to moderate amount of alcohol had a lower risk of developing dementia compared to non-drinkers. Also, people who drank excessively had a higher risk of dementia. They classified a light to moderate level of alcohol as 1-21 units of alcohol per week for men, and 1-14 units per week for women (Deng et al., 2006). One unit of alcohol equals about half a pint of lager, a small glass of wine or a single shot of spirit. Interestingly, they also found dementia risk varied according to the type of alcoholic drink. Light-to-moderate beer consumption was related to a higher risk of dementia, while, light to moderate wine intake was associated with a lower risk of dementia (Deng et al., 2006). One reason why wine intake may be related to a lower risk of dementia is that it contains flavonoids, one of the types of antioxidants we mentioned earlier. It is possible that the alcohol content has nothing to do with the potential benefits (B. R. Ott & Owens, 1998).

In summary, more research is needed to find out whether light to moderate alcohol intake is a safe and effective way to help maintain cognitive function and promote brain health. Of course, drinking alcohol can have significant side-effects and drawbacks for some people for many reasons, and it is certainly not for everyone.

1.2.3.2.3 Sleep

Sleep is another lifestyle factor that has been associated with physical and mental health. There is a lot of evidence suggesting that lack of sleep can affect our attention, concentration, and memory abilities. One study has shown that in elderly people 6 ½ or fewer hours of sleep per night was associated with a higher risk of cognitive decline (Keage et al., 2012). Furthermore, moderate exercise; like the 3 brisk walks per week adopted in this study by the 4 Week Change Challenge and a short nap can help promote the quality of sleep during the night (Tanaka & Shirakawa, 2004). So, the evidence suggests that good quality sleep, and, for most people, more than 6 ½ hours of sleep per night, may be beneficial for cognitive function.

1.2.3.2.4 Smoking

Finally, nowadays it is widely known that smoking has detrimental effects on one's health. It is a risk factor for many diseases, including cerebrovascular diseases and lung cancer. It has also been found that smokers have a higher risk of dementia and Alzheimer's disease, compared to people who never smoked (A. Ott et al., 1998).

The aim of this intervention was to inform participants about the current scientific evidence, by presenting this combination of factors like eating, drinking and sleeping habits as well as (non) smoking. In addition to that, I wanted to offer direct advice that could empower them to lead a positive lifestyle change. In more detail, the message was that they didn't have to give up everything they enjoy eating but, you might like to try some healthier swaps. Moreover, they were advised to consume alcohol on moderation (if any) and get enough good quality sleep as this may help reduce the risk of cognitive decline as we age. Finally, avoid smoking as it is related to an increased risk of developing dementia.

1.2.3.2.5 Mental stimulation

The third week of the course focussed on mental stimulation. Mental stimulation refers to any activity that involves engaging in mental activities. The list of different possible mental activities is long, and includes activities such as reading and writing, playing music, doing puzzles, playing cards or board games, planning and organising. Research has shown that frequent participation in many mentally stimulating activities is linked to a lower risk of Alzheimer's disease (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Wilson et al., 2002). So, increasing the level of mental stimulation can help promote brain health.

The evidence for the benefits of mental stimulation comes from two areas of research. One area has looked at the memory and thinking abilities of people who happen to have a relatively higher level of mental activity in their lives compared to people with a generally lower level of mental activity. The other area of research has looked at what effect introducing new mental activities such as cognitive training, otherwise known as brain training, can have on people in controlled studies.

Research has suggested a protective effect against age-related cognitive decline or dementia for people who happen to have a relatively higher level of mental stimulation in their life. This effect has led to the concept of "cognitive reserve". Research has shown that people with higher levels of education, more intellectually demanding jobs, and greater engagement with mentally stimulating activities tend to have higher levels of cognitive function when they are older and lower risk of developing dementia (Scarmeas et al., 2001).

For example, one community-based study interviewed more than 1,700 healthy people aged 65 and over and followed them for 7 years. They measured how much people participated in leisure activities such as listening to music, visiting friends, being visited by friends, reading, going to movies or sports events, knitting, doing volunteer work, going to church, walking for pleasure or watching television and related this to the risk of developing dementia. It was apparent that leisure activities examined in this study included more than just mental stimulation and included physical and social activities. Researchers found that participation in more than 6 activities was associated with 38% lower risk of

developing dementia. In particular, the mental stimulation activities were linked to the lowest dementia risk when compared to either the physical or social activities (Scarmeas et al., 2001).

Some mentally stimulating activities may contribute to cognitive reserve more effectively than others. The key aspects of these activities appear to be variety, novelty and challenge (Fernandez, 2013). That is, activities that a person might find challenging and involve something new may be particularly effective in staving off the effects of age on cognitive function.

Also, excessive specialisation in one activity is not an ideal strategy for developing cognitive reserve. For example, a study conducted in 1999 showed that doing crossword puzzles more often did not reduce age-related cognitive decline (Hambrick, Salthouse, & Meinz, 1999). Doing the same activity repeatedly becomes routine and it becomes less challenging over time.

It seems that variety is a key aspect of promoting cognitive reserve and a key factor to consider when choosing mentally stimulating activities is effort. For example, writing is more challenging than reading, and playing music is more challenging than listening to music. When people engage in new and more challenging tasks, they encourage more areas of the brain to connect with each other, and this may be a key factor when considering which mentally stimulating activities are most effective for promoting brain health (Fernandez, 2013).

The relationship between some specific activities and cognitive reserve has received some attention. One area of interest is music. Musical training has been shown to be very beneficial for the brain. Musicians appear to have enhanced volume in the brain regions related to vision, perception, movement and hearing (Gaser & Schlaug, 2003). A recent study looked at the relationship between years of musical training and performance on tests of memory, attention and language in older adults. They found that people with any degree of musical training showed better cognitive functioning in advanced age when compared to non-musicians, and those who underwent musical training for 10 years or more showed the best cognitive test performance. The findings also suggested that musical training at any point throughout the lifespan can have a positive effect on cognitive function, so it is never too late to start (Hanna-Pladdy & MacKay, 2011).

Another evidence-based activity is learning and practising a new language. Research has shown that bilinguals are better on tasks of attention and cognitive control (Bialystok, Craik, Klein, & Viswanathan, 2004). Furthermore, in 2007 researchers investigated 184 people with dementia, 93 of whom were bilingual. They found that dementia onset was delayed by 4 years for bilinguals when compared to people who spoke only one language (Bialystok, Craik, & Freedman, 2007). So, learning a new language or a musical instrument could help older adults build cognitive reserve and reduce the risk of developing dementia, but more research in this area is needed.

Another interesting topic which has lately received a lot of interest is cognitive training, or "brain training". This term refers to the regular practice of specifically designed tasks with the goal of

improving some area of cognitive function. There is a variety of computer-based brain training programmes offered these days, that claim to improve memory and thinking abilities. While there is evidence that brain training does produce improved performance on specific tests, so far it does not appear to have a generalised effect on overall cognitive function (Owen et al., 2010). Therefore, a brain training programme might be beneficial but, on its own it cannot provide the variety of mental stimulation that is recommended.

Ageing is a natural process and though not always pleasant, it is normal for some types of cognitive function, like speed of processing and memory to decline as we age. However, increasing one's level of mental stimulation is a good way to help provide some degree of resilience/protection against these changes. Cognitive reserve refers to the protective effect that engaging in a variety of mentally challenging activities that require creativity, dealing with new ideas, and learning new skills can have on brain health, maintaining cognitive function, and delaying the onset of dementia. Consequently, the key aspects to consider when choosing to incorporate more mentally stimulating activities into one's life are variety, novelty and challenge.

First, variety means engaging in several activities regularly. More than 6 leisure activities are recommended but of course, engaging with even one activity is better than nothing. No one mental activity has been shown to be better than another (Stern, 2009). Individuals can incorporate brain training programmes, and puzzles like Sudoku or crosswords, or playing cards or other games, into their regular routine, but at the same time the variety of activities is key, and any type of activity that becomes routine over time also becomes less effective.

Additionally, the desired activities are the challenging and novel, the ones that require some effort. For example, learning a new language, or learn to play a new musical instrument, writing stories or even poetry. Other challenging activities could include singing, joining a reading group or a cinema group, attending a play, a museum, or a concert, planning a trip, or volunteering. When novelty and challenge are combined in an activity then a person will be able to build stronger resilience against the cognitive decline that comes with age.

1.2.3.2.6 Social interaction

The final week of the course focusses on social interaction. The positive effect of good social relationships on mental health has been well described (Kawachi & Berkman, 2001). In addition, studies have shown that participation in social activities is related to better cognitive function in older people (Bassuk, Glass, & Berkman, 1999; Zunzunegui, Alvarado, Del Ser, & Otero, 2003).

Social engagement is defined as participating in a variety of social activities with other people (Bassuk et al., 1999). Most people have what is known as "social network", which consists largely of their friends and family. The number of people in a person's social network can vary greatly between people.

So, social engagement involves both maintaining connections with people in the social network, as well as participating in social activities that involve meeting new people. Social engagement can involve a range of different activities such as book clubs, sports clubs, meeting friends at the pub, or meeting new people at events like family weddings or other social occasions.

In a community-based study in Sweden, researchers interviewed more than 1,000 people who were aged 75 or over and without cognitive decline, about the richness of their social network. They asked people about the size of their social network, how often they contacted the people they knew, and the satisfaction they experienced through these interactions. After 3 years, some of these people were diagnosed with dementia. Interestingly, the people who had few or no social ties, were not married or were living alone had a 60% increased risk of developing dementia compared to people who had close relationships and were married or living with another person. They concluded that a rich social network could act protectively against the risk of developing dementia (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000).

Another study investigated the association between social engagement and cognitive function in healthy older people. Researchers examined social engagement through 3 measures: social network size, support from social ties and frequency of participation in social activities. They found that more frequent participation in social activities and satisfaction from social ties were related to better cognitive function. These factors were found to be more important than the number of contacts in a person's social network (Krueger et al., 2009).

However, besides the potential benefits of having a rich network of social connections and being engaged in social activities, evidence also suggests that when it comes to brain health, some types of social interactions are more beneficial than others (Ybarra et al., 2008).

In one of his studies, Professor Ybarra and his colleagues assigned young participants to one of the following 3 groups: an intellectual activity group, where they completed tasks like crossword puzzles for 10 minutes, a social group where they discussed a social issue for 10 minutes and finally, a control group where participants watched a 10-minute clip of a television programme. After the end of their activities, all participants took a concentration and attention test. The results showed that after just 10 minutes in either the intellectual or social activity group there was a boost in cognitive performance when compared to the control group. Therefore, engagement in intellectual and social interaction was more beneficial for concentration and attention than television (Ybarra et al., 2008).

Furthermore, the more novelty and variety an activity involves, the better. For example, in an American programme called the "Experience Corps", seniors volunteer at schools for 15 hours per week for a full school year and assist children to improve academically and behaviourally. Volunteers undertake various tasks including library functions and mentoring academic activities. A small pilot study showed that participation in this programme led to an improvement in cognitive function in the volunteers. Brain

scanning results also showed that these volunteers had increased brain activity. The researchers concluded that this indicated "measurable brain plasticity" in these volunteers (Carlson et al., 2009). This was a small pilot study, but it showed that increased social and intellectual engagement could have significant positive effects on cognitive function and brain activity.

In conclusion, evidence suggests that the best combination for maintaining brain health is possibly to engage in a variety of social activities that involve some degree of mental stimulation. The course encouraged participants to keep in mind that besides novelty and challenge, they should also engage in satisfying and quality social interactions, with people they enjoy interacting with. For example, try calling a person they haven't spoken to in a while or look for a new social group to join. Joining a new social group is likely to boost social engagement. I also advised them to try a book club, a community group, a religion group or a political group. If they joined a dance group, this would promote both social interaction and physical activity at the same time. Another example was volunteering as several studies have suggested that volunteer work can have a positive impact on well-being and reduce the risk of depression.

After describing the interventions, I will now move on to discuss Apolipoprotein E (ApoE) and its role to AD research.

1.3 Rationale and Aims

As discussed in previous sections, SCD might constitute a risk factor for future cognitive decline and dementia (Jessen et al., 2014). However, SCD is very common and in some cases its aetiology might include normal ageing, the effect of psychological/psychiatric/medical conditions, or the effect of substance use, regardless of the risk of future cognitive decline (Slavin et al., 2010). Despite being a very distressing condition, SCD suffers from the lack of a universally accepted set of diagnostic criteria and a clear definition. Consequently, there is a great need for further investigation in order to explore the characteristics of people dealing with SCD and possibly identify interventions for this population. Furthermore, FCD is also a condition with heterogeneous aetiology which is potentially associated with psychological factors (Pennington, Ball, & Swirski, 2019). It is placed on a spectrum ranging from SCD to dementia and its population is characterised by self-reported memory concerns. Just like SCD, FCD is lacking diagnostic criteria and management startegies (Pennington, Ball, & Swirski, 2019).

For these reasons, one of the aims of this study is to explore the characteristics of people with SCD and FCD, in order to learn more about these conditions. The first research question thus, is "What are the characteristics of people with SCD and FCD?". This question will be answered by examining the demographic characteristics of the SCD and FCD groups and their performance on the cognitive and psychological outcome measures of the DCODE study.

Moreover, evidence regarding the effectiveness of interventions for SCD and FCD is lacking (Stewart, 2012). For this reason, the secondary aim of the DECODE study is to develop and provide a specifically designed intervention for non-demented individuals with SCD and further test its effectiveness, by comparing it against a mindfulness meditation intervention and a control group. The second research question is "Is it possible for people with SCD to benefit from a mindfulness or a lifestyle intervention?". This question will be answered by randomly assigning the participants into three educational groups: mindfulness intervention, lifestyle factors intervention and no-intervention (control) group. Subsequently, I will assess the effectiveness of the interventions by comparing participants' cognitive and psychological outcome measures, based on the group they were assigned into.

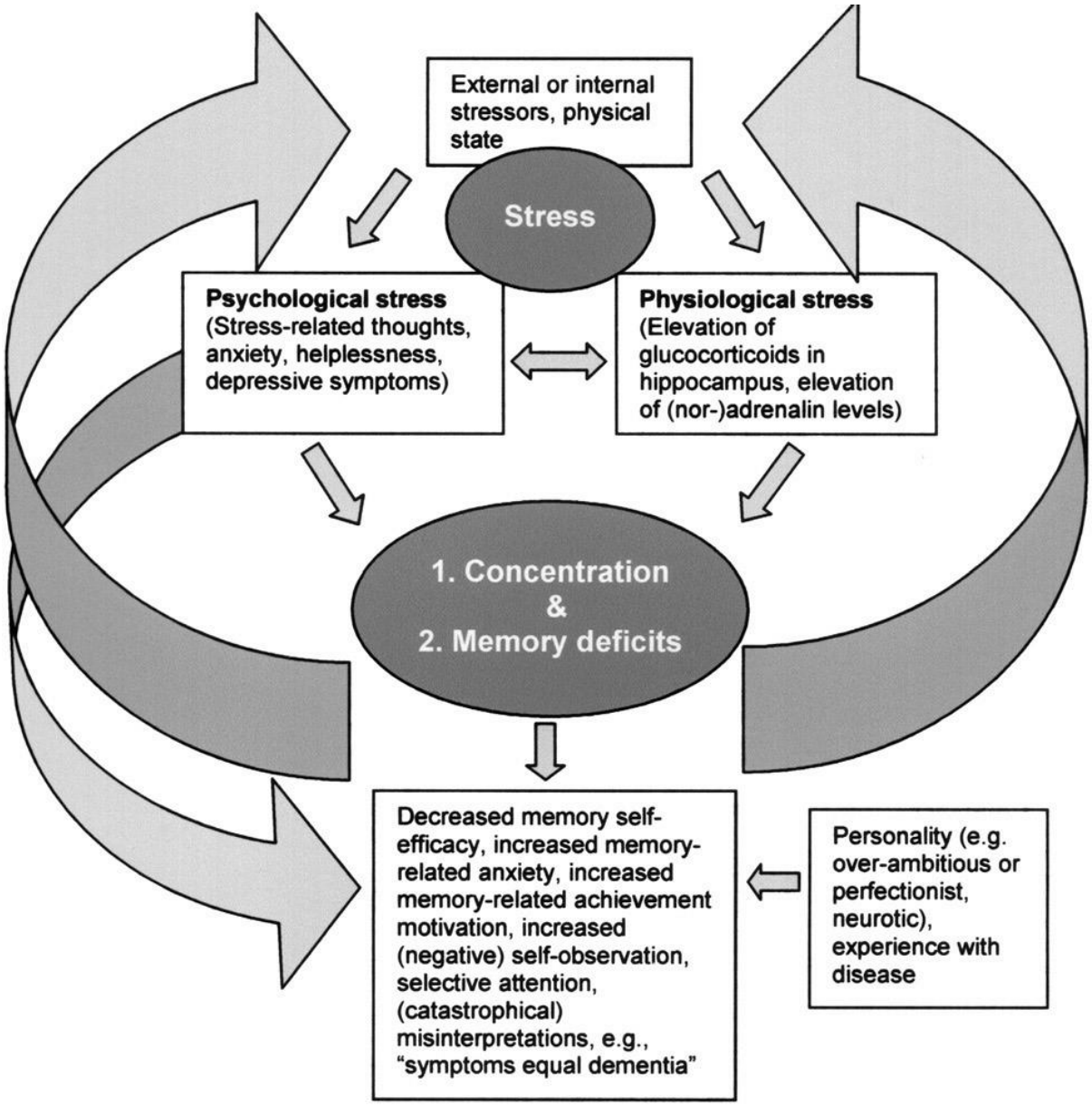

Figure 1.2 Hypothetical model of FCD (Metternich et al., 2009) – adapted from *Behav Res Ther* 28 (1990) 105-117, *J Psychosom Res* 36 (1992) 515-529

The most popular approach of Mindfulness meditation is the Mindfulness-Based Stress Reduction (MBSR) which was developed and brought into health care in the 1980s by Jon Kabat-Zinn (Kabat-Zinn, 1982). The combination of MBSR with elements of cognitive-behavioural therapy (CBT) has led to what is known as Mindfulness-Based Cognitive Therapy (MBCT) which was shown to be an efficient intervention in preventing depression relapses (Teasdale et al., 2000). MBSR involves training through practices like mindful eating and walking, yoga, sitting meditation and the body-scan.

Evidence suggests that mindfulness interventions can help reduce psychological symptoms such as anxiety, stress and depression and help treat pain and eating disorders (Kabat-Zinn, 1982; Kabat-Zinn et al., 1992; Kristeller & Hallett, 1999; Shapiro, Schwartz, & Bonner, 1998; Teasdale et al., 2000).

Despite the fact that its effectiveness has not yet been conclusively established (Baer, 2003), even short-term training in mindfulness has been shown to improve cognitive flexibility and performance on attention tasks (Moore & Malinowski, 2009; Zeidan, Johnson, Diamond, David, & Goolkasian, 2010).

This study aims to examine whether mindfulness meditation training could promote and maintain optimum cognitive function and psychological well-being in people with SCD. The uncertain period between experiencing SCD and receiving a diagnosis of dementia, or being reassured that there is no dementia, can be long and distressing. However, there is little to be offered to this population in terms of support and treatment. In this study I examined if mindfulness training would enhance cognitive function and psychological factors in people with SCD, when compared to a lifestyle intervention and a control group.

Regarding the Lifestyle factors intervention, drawing from the evidence provided in current scientific literature, I designed a 4-week educational programme that presented information relevant for promoting and maintaining optimum cognitive function.

As shown in a prospective cohort study which was set up in Caerphilly in 1979 and aimed to investigate the effect of environmental factors on chronic disease (Elwood et al., 1999a), people who engage in physical and social activities, avoid the excessive use of alcohol, do not smoke and also review their health, can reduce their risk of dementia by up to 60%. A different study conducted in Finland and known as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) suggested that a multidomain intervention which targets modifiable vascular and lifestyle factors like diet, exercise and cognitive training, can help people at-risk to preserve and even improve their cognitive function (Tiia Ngandu et al., 2015). What is also very interesting about the FINGER study is that researchers focused on people who were at predementia and presymptomatic stages, when an intervention might be most effective. Consequently, people with SCD who have not yet any evident symptoms of cognitive deterioration, might benefit the most from such an intervention.

The content of this intervention included a description of factors associated with improved outcome for cognitive function and general health. These are lifestyle factors such as exercise, diet, mental

stimulation and social engagement, which have been linked to reduced risk of developing dementia and to a slower rate of memory decline in normal ageing (Stern, 2009).

Offering computer-based interventions constitutes a challenge as it does not allow researchers to have face-to-face contact with the participants. However, gathering big groups of people at the same place and time for 4 weeks, in order to personally deliver the interventions would have not been feasible. Moreover, this could possibly lead to people dropping out of the study. Consequently, I decided to offer the participants the chance to attend the interventions in the form of online courses.

Lastly, regarding the outcome measures of cognitive and psychological testing used in the DECODE study, I would like to mention that the selection of the tools was based on the routine neuropsychological assessment that is performed in clinical settings.

An exception to this is The Test of Memory Malingering (TOMM; Tombaugh, 1997). This test was added to the cognitive testing battery as one-time assessment of malingering on a simple task of recognition and recall. The rationale behind this is mainly based on cognitive experience suggesting that people with FCD tend to fail the TOMM, even though it is considered to be a fairly easy task even for people with some sort of cognitive impairment (Pace et al., 2019). Moreover, an unpublished preliminary study conducted by a clinician in the research group, found that a small group of FCD patients (N=10) was more likely to fail the TOMM when compared to a small group of people with SCD (N=10). Consequently, I thought that this test might be of great research importance in an effort to better differentiate FCD people from other populations.

The selection of the psychological questionnaires used was based on the variables of interest within the study. Measuring psychological factors like Depression, Stress, Anxiety, Health Anxiety, and factors like Well-being and Readiness to Change, will allow me to answer the research question stated at the beginning of the research project.

1.4 Brief outline of the current study

This study along with the following pilot studies constitute a bigger trial, named "DECODE", which is an acronym for "Development and Evaluation of Interventions in People with Subjective Cognitive Decline".

The DECODE study is a randomised controlled trial which entails the description of a population with memory concerns. Such population is characterised as a group of people with SCD and a second group of people with FCD. The second aim of the study is to explore whether a mindfulness and a lifestyle factors intervention could potentially benefit people with SCD. In order to achieve that, the DECODE

study included several cognitive and psychological outcome measures. It also included optional genotyping for the participants that agreed to offer a blood sample.

Subjects that participated in the study were recruited through three different major referral routes: public advertising, healthy volunteer databases and memory clinic services. Memory clinic services have been used for the identification of FCD patients (who had already received a diagnosis), whereas, SCD participants were recruited through the public and healthy volunteer databases. Even though, routine referrals of people with memory concerns would normally involve GP practices and memory clinics, for the purposes of this research project we have also recruited from the general public and volunteer databases.

The reason behind this was initially the idea that there might be people who are worried about their memory but have not reached out to any services yet. Secondly, this choice served the feasibility of the DECODE study, as the recruited GP practices and memory services had no individuals with the diagnosis of SCD at the time.

Moreover, I wanted to not only describe the SCD and FCD groups, but also compare them in order to gain more knowledge regarding their characteristics. Both groups fall under the umbrella term of people with "memory concerns" but present a different clinical image. Furthermore, individuals who present such memory complaints might be in higher risk of developing future cognitive deterioration. It is also likely that FCD people constitute a sub-group of the SCD population. Consequently, it is of great importance to not only properly identify such individuals, but also to be able to differentiate one diagnosis from another in order to offer the optimal help.

The DECODE design included the recruitment of individuals who are concerned about their memory, specifically people with SCD and FCD, are 45 years of age or older and have not received any dementia diagnosis. All participants attended a baseline assessment, where they completed a set of cognitive tests and psychological questionnaires. Following this visit, all subjects were randomly assigned to one of three groups: mindfulness intervention, lifestyle intervention, or control group. After completing the intervention (or after 4 weeks of waiting for the control group), all participants were invited back for a follow-up assessment, repeating most of the baseline tests and questionnaires. Finally, 6 months later participants were invited again for the last follow-up assessment (Figure 1.3).

The DECODE study also involved am optional blood test, which was performed at any of the three visits, following participant's consent.

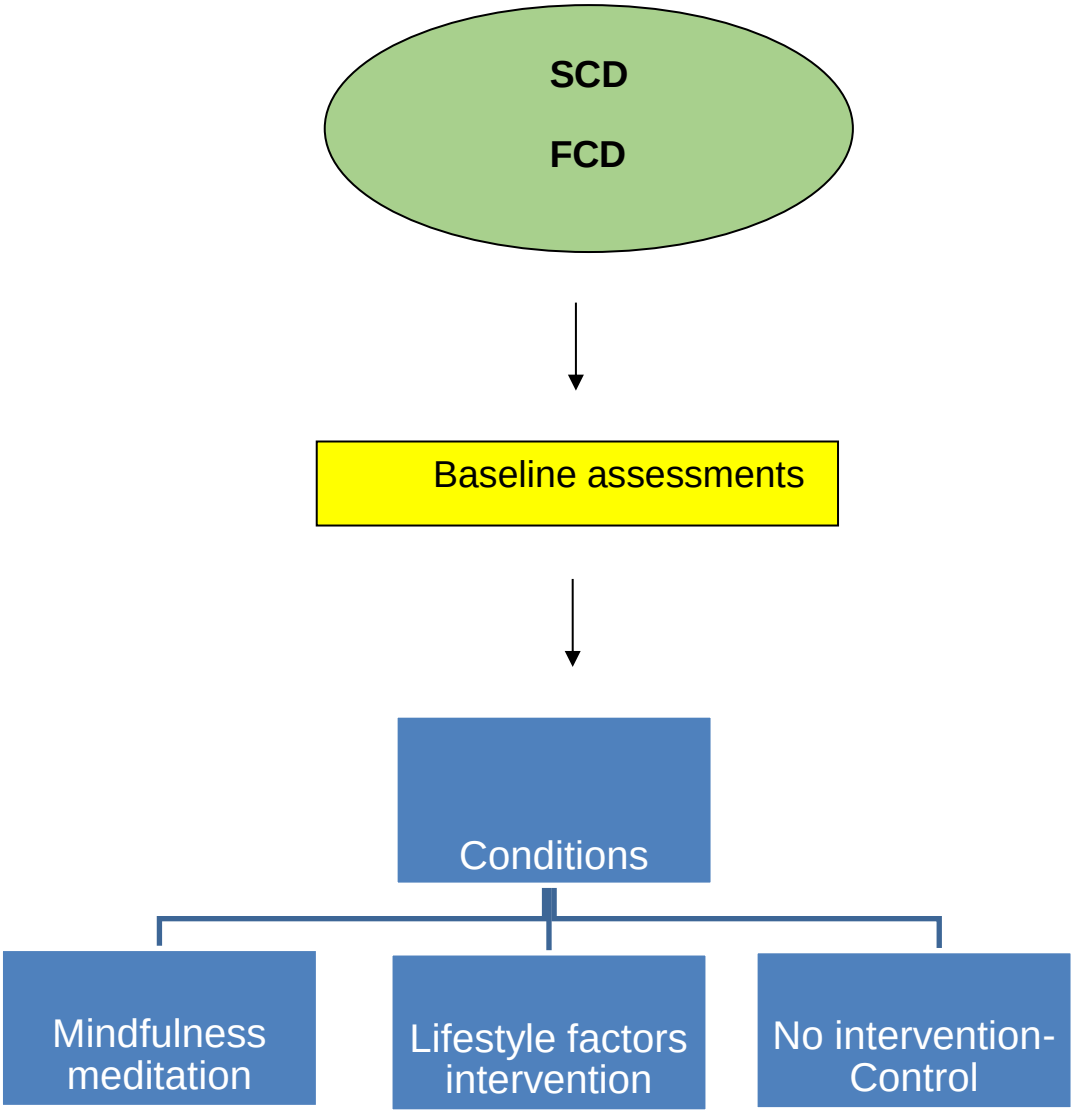

Figure 1.3 Flow diagram of the testing procedure for all participants groups

1.5 Structure of the thesis

Chapter 1 provides a critical review of the current literature regarding all the important conditions, characteristics and ideas that are being examined. It further includes the rationale and outline of the current study and following pilot studies. Chapter 2 is outlining the methodology of the current study. Chapter 3 is the characterisation of SCD and FCD populations. Chapter 4 identifies the effectiveness of the mindfulness and lifestyle interventions for people with SCD. Chapter 5 examines readiness to change, within the context of lifestyle factors for people with SCD. Chapter 6 investigates the ApoE genotype in SCD, in a pilot study. Chapter 7 explores the relations of Health Anxiety to SCD in a pilot study. And finally, Chapter 8 wraps up the findings and discusses limitations of this project and suggestions for future research.

Chapter 2 General Methods

This thesis describes a randomised controlled trial study named DECODE and its findings. This chapter describes the general methods that were used throughout the study. These methods also refer to subsequent chapters.

While most of recruitment and testing were carried out by the author, occasionally some participants were screened and tested by other members of the research group (placement students and honorary assistant psychologists Alice Storey and Saba Meky).

The project has received ethics approval by the South West-Central Bristol Research Ethics Committee and all participants have given their written consent prior to entering the study, according to the Declaration of Helsinki. Funding has been provided by the BRACE charity.

2.1 Participants

2.1.1 Number of participants

Based on an effect size of 0.75 (determined by a review of the effectiveness of mindfulness meditation interventions; Krusche, Cyhlarova, King, & Williams, 2012), an alpha value of 0.05, and power of 0.8 we would require at least 23 participants attending the mindfulness course.

However, this study is exploratory, and it is not possible to calculate the required sample size for statistical significance at this stage. This is because the lifestyle factors intervention is especially designed for the purposes of this study and has never been used before.

As larger samples enable us to evaluate the effects of interest more precisely, we aim to include 30 participants in each of the 3 conditions. Finally, due to expected attrition in a study of this nature (i.e. requiring a considerable commitment and investment of time from each participant), we expect some people to drop out. Consequently, our aim is to recruit 100 participants in total.

2.1.2 Recruitment

The recruitment pathways followed were public advertising (self-referral), the Join Dementia Research service, local GP practices and Memory Services, and the ReMemBr group's Cognitive Disorders Clinic and Healthy Volunteer Database.

The most effective way of recruitment was public advertising. Adverts were published in local newspapers and magazines (the Weekend magazine in the Bristol Post, the Henleaze and Bishopston Voice, the What's on Bristol magazine, the Sunday Independent and the BRACE charity. Posters and

flyers were also put up in the group's Cognitive Clinic (the Brain Centre in Southmead Hospital) and local libraries. All the responders had memory concerns and were aged over 45 years old. From them, 77 people were finally recruited into the study.

Second most effective recruitment pathway was through the ReMemBr group Healthy Volunteer Database. Based at the Brain Centre in Southmead Hospital, the ReMemBr group (Research into Memory, the Brain and dementia) includes neurologists, psychologists and researchers from both University of Bristol and NHS Trust. People who are on this database have expressed an interest in our group's research and have consented to be contacted about any new studies. Potential volunteers were contacted according to their preferred method of contact (email, phone call, letter) and everyone was sent the Participant Information sheet.

More than 100 people were contacted, 17 of whom were eligible and interested in participating. Moreover, 34 people who have signed up with the Join Dementia Research service (JDR) were contacted, but 5 of them were eventually recruited into the study, 2 of whom withdrawn late on. The JDR is an online service where people can self-register their interest in dementia related research. People who sign up might vary from healthy volunteers to people with memory problems or dementia and carers of those. Its purpose is to facilitate recruitment by allowing individuals to be identified as potentially eligible for studies. (The low response number could be explained by the fact that SCD or "memory concerns" are not listed in the specific inclusion criteria when registering a new study). Finally, 8 more people were recruited after another participants' recommendation.

Regarding the Functional Cognitive Disorder (FCD) group, patients were first identified through the Cognitive Disorders Clinic in the Brain Centre. This is a Neurologist led clinic for people with cognitive symptoms. People on the clinic's database who have received the diagnosis of FCD, fulfilled the inclusion and exclusion criteria and had also consented to be informed about research projects, were contacted.

Unfortunately, we did not have a good response rate from memory clinics and GP practices.

2.1.3 Pre-registration evaluations: Inclusion/Exclusion criteria

After identifying a potential participant, their eligibility had to be assessed. This was achieved through a screening phone call. During the phone call participants were assessed regarding their subjective memory concerns and were asked the following: "Are you concerned or worried that you are experiencing significant decline in your thinking abilities more than just normal ageing?" (Smart, Segalowitz, Mulligan, & MacDonald, 2014, p. 15). To continue with the assessment, the person should answer "yes" to this question. For the SCD group this would be enough to classify a person of the general public to have SCD and potentially be included in the study. The aim was to include people

who reported memory complaints but had not necessarily sought any help from memory services. This question was also asked to the FCD patients approached, even though the answer would always be negative as these individuals had already reached out to memory clinics and had undergone a complete neuropsychological assessment before receiving the formal diagnosis.

The next step was the administration of the Adult Pre-Exercise Screening Questionnaire (APSS). This tool assessed whether someone was fit enough to perform a 15-minute brisk walk. We assessed all participants against this task, as the brisk walk was the main task that people in the Lifestyle factors group had to perform. Since participants were randomly assigned into one of the three conditions and we did not know beforehand which group they would join, we had to make sure that everyone would be eligible for all three conditions. In the event of someone having many health risk factors, they were asked to double check with their GP to make sure is safe for them to perform the brisk walk if needed. Participants were also assessed with the Screening Questionnaire (see Appendix) to make sure they don't meet any of the exclusion criteria. They were also asked whether they had done any cognitive testing within the past 3 months. At the end of the phone call, if the person was considered eligible, he was invited to attend the first appointment at the clinic.

Further to this, participant eligibility was determined according to the following criteria:

- In the opinion of the investigator, the participant is capable of understanding and complying with protocol requirements.
- In the opinion of the investigator, the participant is able to physically perform the cognitive tests and is fluent in the language that tests will be administered.
- The participant is aged over 45 years old, expressing concern about cognitive decline (subjective cognitive decline) as per methods of recruitment described above.

Any participant who meets the following criteria did not qualify for entry into the study:

- The person has a current diagnosis or history of any type of cognitive impairment or dementia or has a current diagnosis of neurological/psychiatric disorder or any other diagnosis that significantly affects cognitive performance (including substance abuse).
- The person is incapable of doing a brisk walk.
- The person has been exposed to the cognitive tests performed in this study within 3 months prior to the Baseline assessment.
- The person's score on MoCA test is <20. An individual with a MoCA score this low may have significant cognitive decline (Larner, 2012) and should be referred to their GP.
- The person knows their ApoE genotype.

- The person cannot adequately understand verbal explanations or written information given in English.

2.1.4 The sample

The sample constituted of 100 participants (90 SCD and 10 FCD) who attended the baseline visit (81 of them have also completed visit 2 and 73 have completed visit 3). All participants were above or equal to the age of 45 and expressed subjective memory complaints. There were 33 males and 68 females, whose age varies from 45 years old to 89 years old (M=62.45, SD=9.16) and their years of education vary from 6 up to 24 (M=15.22, SD=3.79). Some of their demographic details are described in Table 2.1 below. Table 2.2 shows some of the participants' scores on cognitive tests at baseline.

Table 2.1 Demographics for all participants

Meditation (Yes/No)	6 (6%)	94 (94%)
Handedness (R/L)	80 (80%)	20 (20%)
Fam. history AD/dementia (Yes/No)	49 (49%)	48 (48%)
Sought help (Yes/No)	27 (27%)	73 (73%)

Table 2.2 Questionnaire scores for all participants

	Mean	**Std. deviation**
CRIq Education	119.09	14.97
CRIq Work activity	117.11	16.88
CRIq Leis. Time	134.52	21.70
CRIq Total	131.28	17.51
MoCA	27.03	2.88
DASS Depression	7.28	8.79
DASS Anxiety	5.03	6.14
DASS Stress	11.33	8.18
DASS Total	23.64	19.68
WHO Total	14.62	4.73

CRIq= Cognitive Reserve Index questionnaire, MoCA= Montreal Cognitive Assessment, DASS= Depression, Anxiety and Stress scale

The participants' assignment to the groups (mindfulness meditation, lifestyle, control) was random in order to achieve equal numbers in the three groups. There are 33 participants in the Meditation group, 34 in the Lifestyle and 34 in the Control (Figure 2.1).

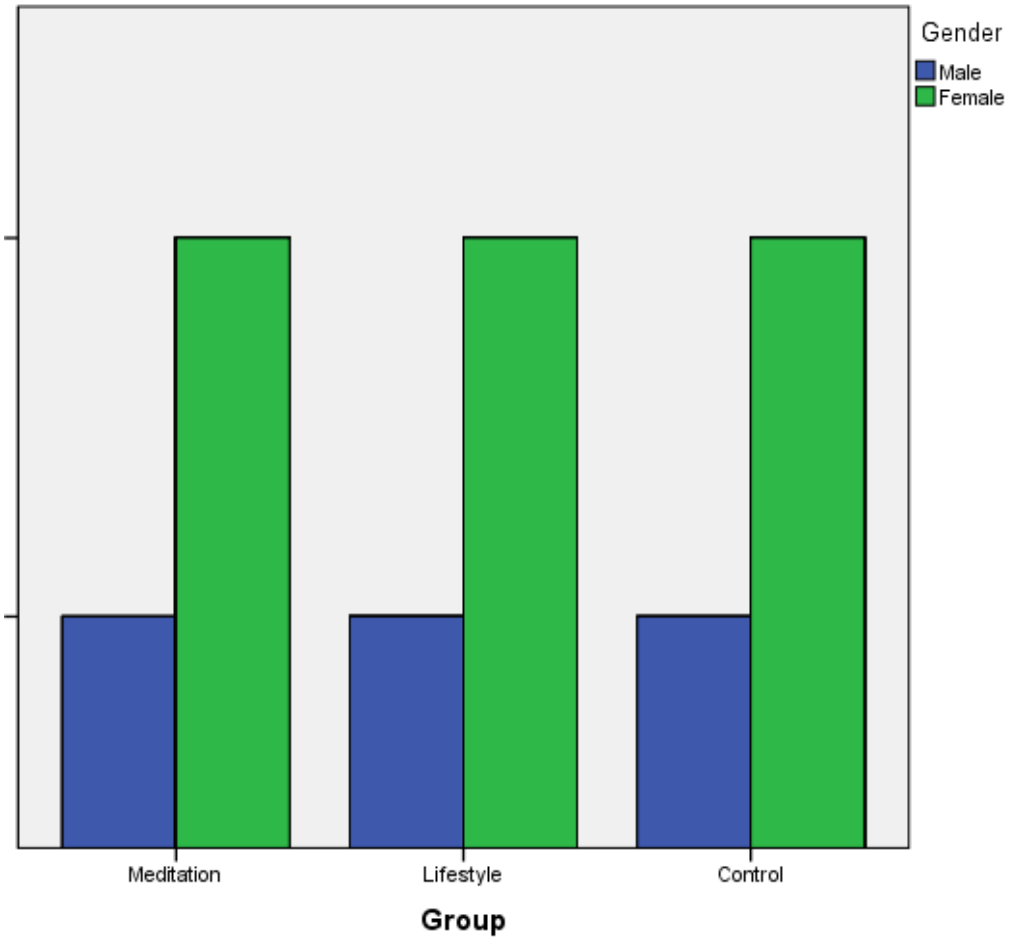

Figure 2.1 Participant distribution across the three groups by gender

2.2 Materials

2.2.1 Cognitive battery and Questionnaires

The materials used in the DECODE study are listed below. The selection of the tools assessing cognitive function has been based on routine neuropsychological assessment that is performed within the clinical setting.

An exception to this is The Test of Memory Malingering (TOMM; Tombaugh, 1997). This test was added to the cognitive testing battery as one-time assessment of malingering on a simple task of recognition and recall. The rationale behind this is mainly based on cognitive experience suggesting that people with FCD tend to fail the TOMM, even though it is considered to be a fairly easy task even for people with some sort of cognitive impairment (Pace et al., 2019). Moreover, an unpublished preliminary study conducted by a clinician in the research group, found that a small group of FCD patients (N=10) was more likely to fail the TOMM when compared to a small group of people with

SCD (N=10). Consequently, I thought that this test might be of great research importance in an effort to better differentiate FCD people from other populations.

The selection of the psychological questionnaires used was based on the variables of interest within the study. Measuring psychological factors like Depression, Stress, Anxiety, Health Anxiety, and factors like Well-being and Readiness to Change, will allow me to answer the research question stated at the beginning of the research project.

A. Background Information questionnaire

This questionnaire was developed for the purposes of this study and was used to collect information regarding the following components: age, gender, area of residence, who do they live with, smoking, alcohol consumption, physical activity level, height, weight, body mass index, meditation practice and general health concerns behaviour. Lastly, there were past medical history questions to include information regarding raised cholesterol, diabetes, stroke, transient ischaemic attack, heart disease, other neurological condition, family history of Alzheimer's or other dementia, history of depression/anxiety, any other psychiatric or medical condition and finally, the use of any medication. This information will help me provide a better description of the populations under investigation (SCD and FCD) and compare them against each other.

B. Tests of Cognitive function

1. Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) - Baseline only.

The MoCA is a 10 minutes and 30-points test designed to detect cognitive impairment and is widely used in clinical practice as it has been shown to be very sensitive to Mild Cognitive Impairment and early Alzheimer's. It assesses the following cognitive domains: memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language and orientation. It is a pen and paper test and the scores are based on the number of correct answers provided by the participant. A higher score means better cognitive function whereas, a lower score might indicate cognitive impairment. There are three tasks at the beginning performed by the participant, that are assessing visuospatial memory and executive functions and the rest of the answers are documented by the administrator.

2. Test of Memory Malingering (TOMM) (Tombaugh, 1997) - Baseline only.

This is a symptom validity test. The participants are shown 50 pictures of common objects during the learning trial (for 3 seconds, at 1-second intervals) and then for the recognition trial, they are presented

with 50 panels that contain a new picture and one of the previously shown target objects. They are asked to select the picture they saw before, and they are given explicit feedback on their responses. One point is given for each correct response (with 50 being the maximum) and if anyone scores < 45 then the second trial was administered as well (same target objects, different order). A higher score means that the person is not malingering whereas, a lower score might indicate memory malingering. Even cognitively impaired patients are expected to score high on this test, and a score below 45 might distinguish individuals who are faking their performance from patient with cognitive dysfunction (Rees, Tombaugh, & Boulay, 2001). The administration time is 15 minutes. It is a pen and paper test that also includes a booklet (with pictures of the objects). All pictures are shown by the administrator and all answers are documented by the administrator. The participant is not allowed to turn any pages.

3. Cognitive Reserve Index Questionnaire (Nucci, Mapelli, & Mondini, 2012) - Baseline only.

This questionnaire is a relatively new tool which evaluates an individual's cognitive reserve based on information regarding their adult life. Cognitive reserve refers to the disjunction between brain pathology and clinical picture, as described by Stern (2009). Besides the total score, it also provides 3 sub-scores: education, working activity and leisure time. The education and working activity scores are just the years that the participant has devoted to education and working life. The leisure time score is calculated by answering how often or rarely the participant has engaged to several activities. The total score is calculated within a formal scoring form provided by the authors. It is a pen and paper test, the administration time is 5 minutes and the participants are completing the answers by themselves. A higher score means better cognitive reserve.

4. Letter Verbal Fluency (Gladsjo et al., 1999)

For this task individuals are given three different letters and are asked to generate as many words as they could in 1 minute. In the first visit we asked them to say words starting from the letters A, N and S, for the second visit we used the letters C, F, and L and for the third visit the letters P, R and W. All answers are written down by the administrator, but only correct answers are scored with one point. Wrong answers or intrusions (words that start with a different letter than the one asked) are being ignored. It is a pen and paper test and a higher score indicates better letter verbal fluency.

5. Semantic category Verbal Fluency (Gladsjo et al., 1999)

During this task, the participant is given a semantic prompt and is asked to produce as many words as possible that belong to this category, in 1 minute. For the first visit we used the category "animals", for the second we used "fruit and vegetables" and for the third we used "articles of clothing". All answers are written down by the administrator, but only correct answers are scored with one point. Wrong answers or intrusions (words that belong in a different category than the one asked) are being ignored. It is a pen and paper test and a higher score indicates better semantic fluency.

6. Rey Auditory Verbal Learning Test (Lezak, 1976, 1983) with the alternate versions of Geffen and Majdan; (Geffen, Butterworth, & Geffen, 1994; Majdan, Sziklas, & Jones-Gotman, 1996)

The RAVLT is a tool used to measure learning, recognition, immediate memory span and susceptibility to interference. Participants listen to a recording with a list of 15 words (List A) and are asked to repeat as many as they can, in any order. The same procedure is repeated over 5 consecutive trials and then the interference list is presented (List B). This list has 15 different words and the participants are asked to repeat as many of the new words as they can recall. Immediately after the end of this trial, the participant is asked to repeat the original list (List A) and then again after 20 minutes (delayed recall). Finally, for the recognition trial the participant is given 50 words and he is asked to recognise which of them were on List A, which of them were on List B and which of them he did not hear at all. The administration time is 25 minutes. All answers are written down by the administrator, but only correct answers are scored with one point. Wrong answers or intrusions (words that do not belong on the lists) are being ignored. It is a pen and paper test that evaluates learning and memory and a higher score means better cognitive functioning in these areas.

7. N-back test - based on (Verhaeghen & Basak, 2005)

The N-back test was used as a Reaction time test to measure how quickly the participants react to a visual stimulus, by pressing a button.

For the N-back test, Presentation software (Version 19.0, www.neurobs.com) was used and it was run either on a Dell laptop with 64-bit Windows 7 or a Toshiba laptop running 32-bit Windows. This computerised experiment was designed by John Grogan who is a Research associate in our research group. The task was based on the study conducted by Verhaeghen and Basak (2005). It has been set up with three blocks of 10 trials, with n=1, 2, 3 for the blocks. The 25% of trials was a target trial, while the rest were randomly chosen. Each trial lasted 2000ms and the digit was shown for 1000ms so there

was an extra 1000ms gap where they can still respond. The numbers shown were 1, 2, 3, 4 and 5. Firstly, participants were asked to do the practice test which was shorter than the main experiment and only for n=1 (1 block of 20 stimuli). During the practice test they were provided with feedback for their responses. After making sure that the instructions were clear, participants would move on to the main experiment which included 3 blocks (n=1, 2, 3; 60 stimuli per block). Instruction were provided on the screen before the beginning of each block, but no feedback was provided. The administration time is approximately 10 minutes. It is a computerised test and all answers are documented by the participants on the laptop. It assesses executive working memory and a faster and correct response indicates better working memory performance.

8. Trail Making Test parts A and B (Reitan, 1955)

This test assesses mental flexibility and task switching, along with attention. For Part A participants are asked to connect with lines 25 numbers in proper order and then 25 numbers and letters in ascending order (Part B). It is a pen and paper test; administration time is 5 minutes and responses in both parts are written down by the participant. A faster and correct performance indicates better motor speed and visual attention.

C. Questionnaires about psychological factors

1. Health Anxiety Inventory (Salkovskis, Rimes, Warwick, & Clark, 2002)

This is a self-report questionnaire for the measurement of health anxiety. In this study we used the short 18-item version which refers to the participants' experiences within the last 6 months. This version also includes two extra subscales which measure avoidance and reassurance behaviours. The main questionnaire requires the participant to circle the statement that better describes them. The avoidance subscale is asking them to rate how likely they are to avoid certain situations (scores ranging from 0 to 8, 0 being "Would not avoid it" and 8 being "Always avoid it"). The reassurance subscale is asking them to rate how often they seek reassurance about their health from various sources ((scores ranging from 0 to 8, 0 being "Never" and 8 being "Daily"). The administration time is 5 minutes. It is a pen and paper questionnaire and participants document their answers themselves. A higher score both in the main section and the subscales, indicates higher levels of Health Anxiety.

2. Five Facets Mindfulness Questionnaire (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006)

This is another self-report questionnaire asking participants to rate certain statements based on how often they are true for them. The five facets examined are acting with awareness, observing, non-reacting and non-judging inner experience, and describing. The administration time is 5 minutes. It is a pen and paper questionnaire and participants document their answers themselves. There is a specific rating pattern, provided by the authors and higher score in any of the mindfulness domains suggests better commitment to the particular facet of mindfulness.

3. Functional Memory Disorder Questionnaire (Schmidtke & Metternich, 2009)

In this study we used the short 10-item version of this questionnaire as it seems better for fast assessment and it also has high accuracy when discriminating FCD patients from healthy controls. This questionnaire is self-reported and has a dichotomous response structure and constitutes of 4 subscales: "Items related to a deficit of working memory and concentration", "Items related to a deficit of the registration of new contents", "Items related to a deficit of retrieval" and "Items related to the variability of symptom severity". The administration time is 4 minutes. It is a pen and paper questionnaire and participants document their answers themselves. The more "Yes" answers they provide, the more likely they are to be at risk of FCD. However, this is a very short questionnaire and it Is not meant to be a stan-alone tool when investigating the diagnosis of FCD.

4. Readiness to change questions, based on the Transtheoretical approach (Prochaska et al., 1994)

Based on this Transtheoretical model, we created this tool which consists of 4 questions. Such tool aims to explore whether a participant is exercising and/or practicing meditation and whether he/she is intending to and has already made a change regarding such activity. It is a self-reported, pen and paper questionnaire and the administration time is 2 minutes. A positive answer indicates the readiness of a person to make a positive change in their lives, by reviewing their exercise and meditation habits.

5. Depression Anxiety and Stress Scale-21 Item version (Henry & Crawford, 2005; Norton, 2007)

This tool was used for measuring depression, anxiety and stress levels in participants. It constitutes of 21 items and participants are asked to rate them depending on how often they applied to them in the

past week. The administration time is 4 minutes, it is a pen and paper questionnaire and participants document their answers themselves. A higher score in the domain of depression, anxiety and stress indicates higher levels of depression, anxiety and stress respectively.

6. WHO Five Well-Being Index (Bech, Olsen, Kjoller, & Rasmussen, 2003)

This last questionnaire is a self-administered tool for measuring current well-being. Participants are asked to rate 5 positive statements depending on how often they applied to them in the past two weeks. The administration time is 2-3 minutes and it is a pen and paper questionnaire. Scores are ranging from 0 to 5 (0= at no time and 5=all the time). A higher score represents better well-being.

D. Measurements of lifestyle factors (Diaries)

All participants were also asked to complete specific Diaries (in the form of structured questionnaires) for one week before starting the 4 weeks course (or 4 weeks of waiting time for the Control group), for one week after completing it and lastly, for one week before coming in for the last visit. The first and second set of Diaries were provided to the participants at the end of their first visit, while the third set was given to them at their second appointment. Such Diaries were designed for the purposes of this study and the aim was to measure the following variables: eating habits, drinking habits (caffeine and alcohol consumption), smoking, exercise (amount and type), meditation, hours of sleep, mental stimulation and social interaction (see Appendix for more details).

All tests and questionnaires were completed individually with an examiner at the Brain Centre, in Southmead Hospital. The initial/baseline assessment included the Background information questionnaire and three extra tests that were not repeated throughout the second and third visit (Montreal Cognitive Assessment, Test of Memory Malingering, Cognitive Reserve Index Questionnaire).

The test results are confidential and were not disclosed to the participants. Only if the test results raised a concern, the participant would be provided with feedback and meet with Dr Margaret who is a Clinical Neuropsychologist. This only happened in one case and, as described in the protocol, Dr Margaret Newson met with the participant to discuss their performance and referred them to their GP for further assessment. Consequently, the participant was withdrawn from the study.

2.3 Blinding-Randomisation

This is a single-blinded study therefore, the examiners were not aware of the participants' group allocation. Dr Margaret Newson performed the randomisation procedure by using the online randomiser http://www.randomiser.org. Dr Newson added in this software the unique participant identification number and the three potential outcomes representing each of the three groups: mindfulness intervention, lifestyle factors intervention and control group. After running the randomisation procedure, each participant number was matched to one of the three groups. Dr Newson later created the appropriate packs for the participants.

Each pack included the group assignment along with the relevant instructions and Dr Newson's contact details in case anyone needed further clarification. Instructions for the two intervention groups included the steps on how to log in and attend the online course, whereas it advised the control group to just wait 4 weeks (that is the duration of the interventions). Instructions also advised participants to complete the diaries that measured activities and habits of daily living, for one week prior to the beginning of the intervention (or the 4-week waiting time for the control group) and for one week after completing it (or after the end of the 4 weeks for the control group). These diaries were handed to the participants by the researcher who performed the cognitive and psychological testing, at the end of the first visit. Dr Newson did not advise any other members of the research team about the group allocation but kept a written record in a locked filling cabinet in the Brain Centre.

2.4 Procedure-Testing

All participants attended three visits at the Brain Center, in Southmead Hospital. At the beginning of the baseline visit they were asked to read the Participant Information sheet (if they hadn't done so already) and they were given the time to ask any questions. Everyone was asked to sign the Consent form at the first visit, and they were made aware that they could withdraw from the study at any point without giving a reason. Participants were offered refreshments during all visits and were also reimbursed for any travel expenses that incurred as a result of their enrolment in the study.

The baseline assessment lasted approximately 1 ½ hours and included the tests and questionnaires described above. At the end of this visit, participants were given an envelope with their group assignment (either an Intervention: Mindfulness meditation or Lifestyle factors course, or the Control group). The second visit took place at least 6 weeks later (4 weeks for the course and 2 weeks for the pre and post intervention diaries), while the third visit was arranged 6 months after the second one. Visits 2 and 3 lasted approximately 1 hour as some of the tests were not repeated during these sessions (Figure 2.2). Both Interventions were delivered as online courses that lasted for 4 weeks while, people

in the Control group were asked to just wait for these 4 weeks as they did not need to do anything different than what they would normally do.

Moreover, the study involved an optional blood test to which participants had consented by ticking the relevant box on the Consent form. The blood sample was obtained by the author at one of the three visits (depending on participant's preference). At the end of the last visit people would reveal their group and the ones who attended an intervention were asked to fill in a feedback form. All participants were reimbursed for any expenses that incurred as a result of taking part in the study.

2.5 Developing the Lifestyle factors intervention

One of the two interventions that were put into the test has been specifically designed for the purposes of this project. This psycho-educational intervention is delivered in the form of an online course for the duration of 4 weeks. There is a video presentation for each week that participants can watch from home on their computer, tablet or phone.

This course is based on evidence from previous studies. For example, according to a study by Sachdev, Lipnicki, Crawford, Reppermund, Kochan, Trollor, Wen, Draper, Slavin, Kang, Lux, Mather, Brodaty, and Sydney Memory (2013) which included people with Mild Cognitive Impairment (MCI), participants who were engaged in mentally stimulation activities were more likely to reverse back to normal cognition.

The main idea is that an intervention offered at an early stage of memory problems/decline could possibly facilitate memory improvement. Moreover, an educational intervention built around lifestyle and relevant modifiable factors could act as a preventative measure against cognitive decline.

According to the Caerphilly study (Elwood et al., 1999a) a person could reduce their risk of developing dementia by up to 60%, by being physically active, socially engaged, avoiding smoking and drinking too much alcohol and eventually, committing to reviewing their health. In addition to that, the FINGER study (Tiia Ngandu et al., 2015) suggested that a multidomain intervention can enable maintaining and even improving the cognitive functions and reduces the risk of cognitive impairment among individuals who are at risk. What is worth highlighting here is that researchers of the FINGER study shifted the focus to pre-symptomatic and pre-dementia disease as well as at -risk stages, when an intervention of this nature can be most effective.

Drawing from the evidence provided in current scientific literature, I developed an online 4-week educational programme which presents information relevant to maintaining optimum cognitive function and promoting brain health. Throughout this programme the participants were also offered direct advice

and ideas of how to incorporate what has been suggested from the literature into their everyday life and eventually follow a healthier lifestyle.

Besides studies like the Caerphilly (Elwood et al., 1999a) and FINGER (Tiia Ngandu et al., 2015), the sources also included books like "The Sharp brains: guide to brain fitness" (Fernandez, 2013), the "Hello brain" website and a 6 steps leaflet for reducing the risk of dementia, produced by Dr Tony Bayer and the Wales Government. The scope of this course was not only to promote a healthier lifestyle but also encouraging positive change. Such an idea is based on the Transtheoretical Model of Change (Prochaska et al., 1994) and aims to promote positive change in everyday habits/day to day living. For this reason, the course was named "The 4 Week Change Challenge".

During the first week of the 4 Week Change Challenge, participants were presented with the element of Physical exercise. In this video the importance of exercise was explained and specifically, the role of aerobic exercise in living a healthy lifestyle. In this first presentation, besides the evidence, participants were also given the task of a 15-minute brisk walk 3 times per week (as a minimum) for 4 weeks, that is the duration of the course. In case people were already physically active they were encouraged to carry on with it during the study. Participants in this group were also instructed to keep track of the number of brisk walks they did every day for the 4 weeks that they were attending the course. The physical exercise element remained the same for the whole course and each week a new component was added while they were reminded to carry on with their brisk walks.

In the second week, participants attended a video about Diet and related factors. The overall aim of this video was to help them follow dietary and drinking habits that would potentially benefit their brain health. Even though there are not any definite conclusions on the specific types of food that can affect cognition, it has been suggested that when it comes to brain, just like with the heart, certain types of food are better than others. Everyone was mostly encouraged to try some healthier swaps that could potentially provide a cognitive boost, rather than giving up everything they enjoy eating. In the same week's video, the debate around caffeine was also mentioned, along with the importance of avoiding smoking and having good quality sleep.

The component added in the third week was mental stimulation. It has been proposed that engagement in mentally stimulating activities can promote brain health and help build resilience against neurodegeneration (Fernandez, 2013). Such stimulation refers not only to engagement with many activities, but also seeking out for the key aspects of variety, novelty and challenge.

During the last week of the course, participants were presented with the concept of social interaction. In this video the aim was to highlight the importance of maintaining frequent interactions and warm relationships with people in their social network. It was also mentioned how important it is to step out of the comfort zone and look for challenge and variety in social interactions, in the same way suggested for mentally stimulating activities.

Finally, participants were given specific examples of activities (like joining a dance club) that could simultaneously challenge the brain and offer a cognitive boost by touching on all areas of psychical activity, mental stimulation and social interaction.

2.6 Compliance with the Interventions

Compliance with the Interventions was only measured for the Lifestyle group. All participants in the Lifestyle group were asked to perform a 15-minute brisk walk, at least three times per week for the duration of the course (4 weeks). In the envelope they received at the baseline visit, I had included a Physical Activity Sheet for documenting the amount of brisk walking they would do each week.

All participants performed at least 45 minutes of brisk walking per week so, they were indeed devoted to the intervention. However, the standard deviation was quite high, showing that there was a lot of variance among them. The mean amount for the first week was 186 minutes (Std. Deviation= 115.11), for the second week 185.90 (Std. Deviation= 161.87), the third week it was 185.77 (Std. Deviation= 162.29) and the fourth week it was 172.23 (Std. Deviation= 145.38).

Unfortunately, I did not measure compliance for the Mindfulness group, as there was not a standard amount of practising time proposed in the online course. In the future, it would be useful to measure compliance for different types of interventions in an objective way, instead of self-reports. This is further discussed in the last chapter of this dissertation.

Chapter 3 Functional Cognitive Disorder and how it relates to Subjective Cognitive Decline in the DECODE study

3.1 Introduction

As part of the DECODE study (Development and Evaluation of Interventions in People with Subjective Cognitive Decline), a group of people with Subjective Cognitive Decline (SCD) and a group of people with Functional Cognitive Disorder (FCD) were identified. The FCD participants had already visited the Cognitive Memory clinic at the Brain Centre (Southmead hospital), prior to the start of the DECODE project and had received the diagnosis of Functional Cognitive Disorder (FCD).

Since both conditions are under-studied, my aim is to understand both populations a little bit more and contribute to the research community's effort to identify people who are at risk of developing dementia, at the earliest stage possible. In this chapter, I will discuss the FCD patients' characteristics and compare them to participants with SCD, recruited from the community.

3.1.1 Functional Cognitive Disorder

Functional Cognitive Disorder (FCD) is a condition in which people present with memory complaints. As discussed earlier, memory complaints might be prodromal to a neurological or psychiatric disorder but quite often, people who report them cannot be diagnosed with a medical condition (Metternich et al., 2009). In this study I used the term Functional Cognitive Disorder (FCD) as described by Pennington and colleagues (Pennington, Hayre, Newson, & Coulthard, 2015).

Patients with FCD might constitute a subgroup of people with SCD, as they also present with self-reported memory complaints and will normally perform within the normal limits on cognitive and neuropsychological examination (Metternich et al., 2009). However, one difference between these two populations is that people with FCD might suffer a lot in their everyday lives, not only due to their typical memory failures like forgetting names, appointments or problems with concentration but also, due to the emotional burden of those (Metternich et al., 2009).

FCD is distinct from SCD as it manifests more severe symptoms and a discrepancy between the subjective experience and the objective observation of functioning. People with FCD also tend to be more resistant to reassurance that their cognition is unimpaired. Moreover, another issue with these two cognitive diagnoses is that SCD seems to be quite common whereas, the prevalence of FCD is still being examined (Pennington et al., 2019).

One theory about the cause of FCD is that when patients notice that their memory and attention lapses, they tend to feel anxious, embarrassed, angry and afraid of dementia. This leads to heightened levels of stress that ultimately might trigger more memory failures (Metternich et al., 2009). Unfortunately, little

is known about the traits of FCD patients so far, but in this chapter, I am attempting to further understand this diverse group by examining a small sample of patients who participated in the DECODE study.

Some studies suggest that between 6% and 12% of the people seen in memory clinics fall under the FCD category (Almeida, Hill, Howard, Obrien, & Levy, 1993; Berrios & Hodges, 2000; Weiner, Bruhn, Svetlik, Tintner, & Hom, 1991) while another report from the ReMemBr group memory clinic in North Bristol Trust mentions that one third of their patients below 60 years of age who have visited the clinic have received a final diagnosis of FCD (Pennington, Newson, et al., 2015).

Even though FCD has been gaining some clinical and research interst, it is yet fairly understudied without any available treatment suggestions. The FCD symptoms have been compared to the model of somatoform disorder (Berrios & Hodges, 2000; Sharpe, Peveler, & Mayou, 1992; Warwick & Salkovskis, 1990) where patients typically have a source of psychosocial stress that could be the initial cause of their memory problems (Schmidtke, 1995). Such stress could derive from major traumatic life events (like the loss of a loved person) or other situations linked to chronic stress, which triggers more memory failures and the sufferers end up in a vicious circle that do not know how to break (Berrios & Hodges, 2000; Sharpe et al., 1992; Warwick & Salkovskis, 1990). An adapted version of somatoform disorders model that could possibly describe FCD.

Some of the features that FCD and somatoform disorders share is the fear of the patient that they have an organic disease, their low spontaneous recovery and moreover, their request for repeated tests and examinations (Schmidtke & Metternich, 2009).

It is interesting to mention here that another of the FCD patients' characteristics is the lack of impairment on neuropsychological tests of memory and attention, as they generally perform within the normal range despite the everyday problems they report, like forgetting colleagues' names or appointments (Berrios & Hodges, 2000; Schmidtke, 1995). People with FCD report at least one or more distressing symptoms that cause difficulties in everyday living, but such symptoms do not progress over time and cannot be better explained by a psychiatric, neurological or general health condition (Pennington, Newson, et al., 2015).

Moreover, some FCD patients seem to be quite anxious about their memory performance and have lower memory self-efficacy compared to people without memory concerns (Ponds & Jolles, 1996). Personality factors like memory perfectionism is usually observed among FCD patients, as they appear to have exaggerated (memory-related) expectations (Berrios & Hodges, 2000; Metternich et al., 2009).

3.1.2 Subjective Cognitive Decline

The link between memory complaints in people without dementia and the future risk of developing the disease has led to the conduction of several studies (Clarnette, Almeida, Forstl, Paton, & Martins, 2001).

Even though some studies have reported no relationship between SCD and objective cognitive decline (Jorm et al., 1997; Riedel-Heller, Matschinger, Schork, & Angermeyer, 1999), others have found that people who complain about their memory might have a higher risk of developing Alzheimer's disease (AD) than those who do not complain, even in the absence of evident cognitive disfunction (Clarnette et al., 2001; Geerlings, Jonker, Bouter, Ader, & Schmand, 1999).

However, subjective memory complaints are very common especially among older people and sometimes might consist part of normal ageing or might be due to other factors such as neurological conditions, medication or substance use effects, or health anxiety and depression (Slavin et al., 2010). For this reason, it is important to further understand SCD as it constitutes a condition with high clinical relevance. Understanding the characteristics of people with SCD and identifying them at the earliest stage possible, could potentially help clinicians prevent AD or intervene before irreversible neuropathological changes occur.

3.2 Objectives

SCD and FCD are both characterised by a subjective worsening of memory and thinking abilities. The aim of this chapter is to describe the demographic, cognitive and psychological characteristics of a small group of FCD patients and compare them against people with SCD who also participated in the DECODE study.

3.3 Participants

As described previously in General Methods, all participants were recruited as part of the DECODE study. The main recruitment method for people with SCD was public advertising (adverts were featured in newspapers and local libraries), the ReMemBr group's healthy volunteer database and the Join Dementia Research service. All FCD patients who participated in the study had already received a formal diagnosis and were recruited through the Cognitive clinic at the Brain Centre, in Southmead hospital. Before contacting a potential participant, I discussed with their neurologists to make sure that they would be eligible for participating. In addition to that, potential participants would go through a screening phone call (in the same way that has been described in General Methods). During this phone call the researchers would go through the Participant Information sheet and explain what the study involves. They would also go through a short screening questionnaire to make sure that the participants didn't have any major psychiatric or neurological condition that would exclude them from participation. Additionally, during the phone call I made sure that participants didn't know their ApoE genotype. Lastly, the Adult Pre-Exercise Screening was administered over the phone in order to make sure that everyone entering the study would be eligible for a 15-minute brisk walk, 3 times per week, in case they

were assigned to the Lifestyle intervention group. After making sure that the individual was eligible for participation, they were invited to attend the baseline visit.

In total, I approached 20 patients who were on the database and fulfilled the inclusion criteria: having a diagnosis of FCD, no major psychiatric or neurological condition and being capable of performing a brisk walk (in case they were recruited into the Lifestyle group that included the task of brisk walking).

From the 20 patients contacted, 15 agreed to participate. However, only 11 of them came to the baseline visit, 9 of whom attended the second visit (1 participant was lost to follow-up and 1 participant could not continue due to health issues). Between visit 2 and visit 3, 1 more participant dropped out (lost to follow-up, did not return messages) and finally, 8 FCD participants completed the study. From the overall statistical analysis though, 1 participant was excluded, as his diagnosis of FCD was not secure and was likely to be changed. Table 8.1 depicts demographic data for all participants (N=10) at baseline.

3.4 Tasks and procedure

At the baseline visit, participants met with me or the other two researchers and were given the time to ask any questions before signing the consent form. We would then proceed with the Background Information questionnaire and the cognitive tests. Following that, they were given a list of psychological questionnaires to complete. A complete list of the cognitive battery and the psychological questionnaires has been provided in General Methods.

Lastly, participants were asked if they wanted to do the (optional) blood test. If the participant had consented to the ApoE test, this could be done at any of the three visits. At the end of the baseline assessment, everyone was given the envelope with their group assignment and the diaries they would have to complete for one week before starting their intervention and for one week after completing it (same would apply for the Control group with 4 weeks interval, which is the duration of the interventions). More information on the testing procedure and the outcome measures can be found in General Methods.

3.5 Results

This section includes descriptive information about both the SCD and FCD groups and between-group comparisons regarding cognitive and psychological outcome measures.

3.5.1 Demographic data

Table 3.1 depicts the demographic characteristics and background information of the DECODE participants per group (SCD and FCD). Most participants are females and their educational level is slightly higher (15.29 years for the SCD and 14.80 years for the FCD) than what has been reported in

previous similar studies. Furthermore, compared to the study by Balash et al. (2013), a smaller percentage of the sample are smokers (2.2% for the SCD and 0% for the FCD versus 9.9%) and more of them are exercising (80% for both SCD and FCD versus 76.7%). These differences however might be attributed to the different samples.

Another interesting point is that 53.3% of the SCD group had family history of dementia or AD (for FCD this was only 10%) which is close to the 60% reported in a study that described the characteristics of people with subjective memory loss in Western Australia (Clarnette et al., 2001).

Regarding the rest of the demographic variables, majority of both SCD and FCD people and especially tend to be overweight, right-handed without medical problems like, high blood pressure, high cholesterol, diabetes or heart disease. None of them has suffered a stroke and only 1 FCD participant had experienced a Transient ischaemic attack (TIA). Moreover, a few of people with SCD them had sought help for their memory in the past 18.9%, contrary to the 100% of FCD patients who had already gone through a clinical examination.

Lastly, almost half of them (40% for both SCD and FCD) had a history of depression but not a history of anxiety and a small percentage of SCD participants had a history of psychiatric (6.7%) or neurological (5.6%) condition (this was 0% for FCD).

Table 3.1 Demographic data for SCD and FCD groups

	SCD (N=90) Mean (SD)	**FCD (N=10)** Mean (SD)
Age	63.07 (9.19)	57.40 (7.83)
Education (years)	15.29 (3.95)	14.80 (2.10)
Gender (M/F)	28/61 (31.1%/68.9%)	4/6 (40%/60%)
Work status (Working/Retired/Currently not working)	46/41/3 (51.1%/45.6%/3.3%)	10/0/0 (100%/0%/0%)
Area (Urban/Suburban/Rural)	36/37/17 (40%/41.1%/18.9%)	1/5/4 (10%/50%/40%)
(Smoker/Ex-smoker/Never smoked)	2/30/58 (2.2%/33.3%/64.4%)	0/1/9 (0%/1%/9%)
Alcohol (units/week)	8.39 (11.40)	6.40 (7.28)
GP visits (past year)	2.79 (2.45)	4.9 (3.51)
Exercise (Y/N)	72/18 (80%/20%)	8/2 (80%/20%)
BMI Interpretation (Healthy/Overweight/Obese/Missing)	35/39/15/1 (38.9%/43.3%/16.7%/1.1%)	0/7/3/0 (0%/70%/30%/0%)
Sought help before (Y/N)	17/73 (18.9%/81.1%)	10/0 (100%/0%)
High blood pressure (Y/N)	17/73 (18.9%/81.1%)	0/10 (0%/100%)
High cholesterol (Y/N)	27/61/2 (30%/67.8%/2.2%)	2/7/1 (20%/70%/10%)
Diabetes (Y/N)	7/83 (7.8%/92.2%)	0/10 (0%/100%)
Stroke (Y/N)	0/90 (0%/100%)	0/10 (0%/100%)
TIA (Y/N)	0/90 (0%/100%)	1/9 (10%/90%)
Heart disease (Y/N)	8/82 (8.9%/91.1%)	1/9 (10%/90%)
Depression history (Y/N/Don't know)	36/53/1 (40%/58.9%/1.1%)	4/6 (40%/60%)
Anxiety history (Y/N)	22/68 (24.4%/75.6%)	1 3/7 (30%/70%)
Family history of AD/dementia (Y/N/Don't know)	48/40/2 (53.3%/44.4%/2.2%)	1/8/1 (10%/80%/10%)
Psychiatric condition (Y/N)	6/84 (6.7%/93.3%)	0/10 (0%/100%)
Neurological condition (Y/N)	5/85 (5.6%/94.4%)	0/10 (0%/100%)
Handedness (R/L)	71/19 (78.9%/21.1%)	9/1 (90%/10%)

BMI= Body Mass Index, TIA= Transient Ischaemic Attack.

As discussed earlier, the aim of this chapter is to compare the FCD and SCD groups in order to better understand their relationship. To achieve this, I compared the two groups with regards to demographic variables, cognitive neuropsychological tests and psychological and lifestyle questionnaires.

For the analysis, I run independent samples t-tests for the numeric variables and a chi-square for the nominal ones.

As shown in Table 3.2, when compared to people with SCD, the FCD patients were more likely to be overweight $x^2(2) = 6.68$, $p = .035$. Moreover, FCD patients are more likely to meditate $x^2(2) = 11.41$, $p = .003$ and for longer time $t(97) = -2.85$, $p = .005$, compared to SCD participants.

Additionally, FCD patients had visited their GP more often than the SCD group in the past year $t(98) = -2.47$, $p = .015$ and lastly, SCD people were more likely to have a family member with dementia $x^2(2) = 7.63$, $p = .022$.

Table 3.2 Comparison of demographic data for SCD and FCD groups

Variable	SCD= 90 Mean (SD)	FCD= 10 Mean (SD)	p-value
Age	63.70 (9.19)	57.40 (7.83)	.064
Gender (M/F)	28/62	4/6	.568
Years of education	15.33 (3.96)	14.80 (2.10)	.678
Alcohol units/week	8.39 (11.40)	6.40 (7.28)	.592
Exercise (Y/N)	71/18	8/2	.945
Aerobic exercise (mins/week)	92.89 (133.70)	99 (172.08)	.894
BMI*	26.55 (4.93)	28.55 (2.72)	.211
BMI* Interpretation (Healthy/Overweight/Obese)	41.6%/39.3%/19.1%	0%/70%/30%	.035**
Meditation (Yes)	3.3%	30%	.003***
Meditation (minutes)	3.20 (23.55)	32.00 (66.63)	.005***
GP visits (past year)	2.79 (2.45)	4.90 (3.51)	.015**
Depression history (Yes)	40%	40%	.945
Anxiety history (Yes)	24.4%	30%	.700
Family history of AD/dementia (Yes)	53.3%	10%	.022**

*BMI= Body Mass Index

**$p<0.05$

***$p<0.01$

3.5.2 Normative data

Even though there is not a lot of information about people with SCD and FCD, it was expected that both groups would perform within the normal range and their scores would not show any objective cognitive impairment. In order to examine whether this assumption would be true for the DECODE study sample, I transformed where possible, some of their scores into T-scores and compared them against the normative data available. The T-scores are standardised scores that will show how far the participants' raw scores deviate from the mean score of a healthy sample, after correcting for age and education. In more detail, 40-60 is considered to be the average range of a T-score.

The T-scores were calculated for the Trail Making Test (Parts A and B), the Rey Auditory Verbal Learning Task (RAVLT; total score and short delay), semantic fluency test (category "Animals") and letter fluency test (letters F, A and S) according to (M Mitrushina, 2005). The score for letter F was extracted from the MoCA (Montreal Cognitive Assessment) test and added to the letters A and S that were used to assess letter fluency at baseline. The scores are presented in Table 3.3.

Table 3.3 T-scores of participants' cognitive tests

	SCD (N= 90) T-score Mean (SD)	**FCD (N= 10)** T-score Mean (SD)
RAVLT total	44.98 (11.28)	45.07 (10.97)
RAVLT short delay	45.48 (10.50)	49.97 (10.33)
Trail A	57.97 (8.75)	51.95 (10.07)
Trail B	58.59 (11.60)	53.40 (13)
FAS	53.92 (9.18)	51.20 (12.07)
Animals	56.01 (10.67)	52.50 (7.78)

RAVLT= Rey Auditory Verbal Learning Test (total score and short delay score), Trail A= Trail Making Test A, Trail B= Trail Making Test B, FAS= letters F, A and S to measure letter fluency, Animals= category of Animals to measure semantic fluency.

Moreover, I compared participants' cognitive function as measured by the MoCA test, against the normative data available (Borland et al., 2017). This has been depicted in Table 3.4.

Table 3.4 Normative data and DECODE scores for MoCA

		Normative Mean (SD)	**SCD (N= 90)** Mean (SD)	**FCD (N= 10)** Mean (SD)
MoCA	Visuospatial	4.1 (1.0)	4.51 (0.77)	4.70 (0.48)
	Naming	2.9 (0.3)	2.92 (0.31)	3.00 (0.00)
	Abstraction	1.7 (0.6)	1.81 (0.45)	1.90 (0.32)
	Delayed recall	3.1 (1.3)	3.80 (1.07)	3.20 (0.92)
	Orientation	6.0 (0.2)	5.92 (0.27)	5.90 (0.32)
	Total	26.0 (2.3)	27.29 (2.06)	26.70 (2.16)

MoCA= Montreal Cognitive Assessment (Cognitive domains: Visuospatial abilities, Naming, Abstraction, Delayed recall, Orientations and Total score). Please note that the subscales of Attention and Language have not been included in this table.

Finally, I compared the sample's performance on the Depression, Anxiety and Stress Scale (21 items) to the existing normative data. More specifically, I compared the scores to the ones presented in Crawford et al. (2009). The comparison between the normative data and the DECODE participants is presented in Table 3.5

Table 3.5 Raw DECODE scores for DASS-21

		Normative Mean (SD)	**SCD (N= 90)** Mean (SD)	**FCD (N= 10)** Mean (SD)
DASS	Depression	3.18 (4.16)	3.76 (4.37)	2.70 (4.60)
	Anxiety	2.25 (3.34)	2.56 (3.19)	2.20 (2.30)
	Stress	5.16 (4.44)	5.94 (4.16)	5.30 (4.50)
	Total	10.59 (10.61)	12.26 (9.90)	10.20 (10.51)

DASS= Depression, Anxiety and Stress Scale (21 items).

3.5.3 Cognitive Neuropsychology outcome measures

As mentioned earlier, I also compared the FCD and SCD groups on their performance on the outcome measures of cognitive neuropsychology variables, using independent samples t-tests and chi-square for the Test of Memory Malingering (TOMM). For the purposes of the analysis, I have classified TOMM results as either "pass" (Trial 1 >45) or "fail" (Trial 1<45).

FCD patients had a higher rate of failure on the TOMM test, $x^2(1) = 14.62$ $p<.001$.

Results are illustrated in Table 3.6.

Table 3.6 Mean scores of Cognitive Neuropsychology and Cognitive Malingering outcome measures

Cognitive Tests			
	SCD= 90 Mean(SD)	**FCD=10 Mean(SD)**	**p**
CRI_q	132 (17.26)	126.8(19.44)	.372
MOCA	27.30 (2.06)	26.70 (2.16)	.396
TOMM fail	2.2%	30%	.000***
RAVLT LD	8.40 (3.35)	9.80 (2.20)	.215
Trail A	28.90 (9.51)	32.40(11.82)	.290
Trail B	71.20(30.18)	76 (34.22)	.640
Letter fluency	40.50 (9.25)	37.4 (11.20)	.313
Semantic fluency	21.60 (5.18)	20.9 (2.96)	.657
N3 react time	809.3 (183.61)	863 (77.43)	.388
N3 accuracy	76.6 (7.02)	75 (5.33)	.500

**Abbreviations for Cognitive tests (for the extended list and references, please see chapter General Methods):* CRI_q = Cognitive Reserve Index questionnaire, MOCA = Montreal Cognitive Assessment, TOMM fail = Test of Memory Malingering fail, RAVLT LD = Rey Auditory Verbal Learning Test-Long Delay (correct words recalled), Trail A= Trail Making Part A (seconds), Trail B= Trail Making Part B (seconds), Letter fluency = Letter fluency test (total correct answers), Semantic fluency = Semantic fluency test (total correct answers), N3 react time = N-back test (N=3) reaction time, N3 accuracy = N-back test (N=3) accuracy

**p<0.05

***p<0.001

3.5.4 Psychological and Lifestyle questionnaires

Lastly, I compared the FCD and SCD groups on their performance on the outcome measures of psychological and lifestyle variables. In order to achieve this comparison, I performed independent samples t-tests.

The two groups were significantly different on the Non React variable of the Five Facets Mindfulness questionnaire t (98)= -2.06, p= .042.

Results are illustrated in Table 3.7.

Table 3.7 Mean scores of Psychological and Lifestyle questionnaires

Psychological Questionnaires			
	SCD= 90 Mean(SD)	**FCD= 10 Mean(SD)**	**p**
Health Anx	13.60 (5.90)	11.50 (6.12)	.290
FFMQ Obs	25.58 (5.70)	26 (8.02)	.832
FFMQ Descr	27.20 (6.59)	26.80 (6.84)	.848
FFMQ Act	24.19 (5.60)	24.10 (7.85)	.964
FFMQ Nonju	28.07 (6.06)	28.70 (7.36)	.759
FFMQ Nonre	21.03 (5)	24.60 (6.75)	.042**
FMDQ Total	6.26 (2.22)	6.80 (3.32)	.488
DASS D	7.39 (8.77)	5.40 (9.19)	.499
DASS A	5.09 (6.33)	4.40 (4.60)	.739
DASS S	11.47 (8.16)	10.6 (9)	.752
DASS Total	23.96 (19.74)	20.40 (21.01)	.593
WHO Total	14.66 (4.75)	14.50 (4.99)	.922

**Abbreviations for Questionnaires (for the extended list and references, please see chapter General Methods):* Health Anx = Health Anxiety Inventory, FFMQ Obs = Five Facets Mindfulness Questionnaire Observe, FFMQ Descr = Five Facets Mindfulness Questionnaire Describe, FFMQ Act = Five Facets Mindfulness Questionnaire Act with Awareness, FFMQ Nonju = Five Facets Mindfulness Questionnaire Nonjudge, FFMQNonre = Five Facets Mindfulness Questionnaire Nonreact, FFMQ Total = Five Facets Mindfulness Questionnaire Total, DASS D = Depression Anxiety and Stress Scale-Depression, DASS A = Depression Anxiety and Stress Scale-Anxiety, DASS S = Depression Anxiety and Stress Scale Stress, DASS Total = Depression Anxiety and Stress Scale Total, WHO Total = WHO Five Well-Being Index Total.

**$p<0.05$

3.6 Discussion

3.6.1 Demographic data

The main aim of this chapter was to describe the sample of the DECODE study which includes people with SCD and a small group of people with FCD and compare the groups against each other. It was observed that most participants were highly educated females, who were mostly non-smokers and physically active (Table 3.1).

The majority of the SCD group had a family history of dementia or AD. This observation is in accordance with a study describing the characteristics of people with subjective memory impairment, in Western Australia. This study reported that 60% of the sample had dementia or AD family history (Clarnette et al., 2001).

Regarding the rest of the demographic variables, majority of both SCD and FCD people and especially tend to be overweight, right-handed without medical problems like, high blood pressure, high cholesterol, diabetes or heart disease. Moreover, a few of people with SCD had sought assistance related to memory concerns, compared to FCD patients who had already gone through a clinical examination. Lastly, almost half of the participants had a history of depression.

The comparison of the two groups regarding demographic data, revealed significant differences between FCD and SCD participants on several demographic variables. Firstly, FCD patients were more overweight than the SCD group. Moreover, more of them were meditating at baseline in comparison to the SCD people. Lastly, people in the FCD group reported more visits at the GP in the last year and were less likely to have family history of dementia or AD, compared to people with SCD.

Unfortunately, little is known about FCD and there are not any studies looking at the characteristics of FCD patients. Consequently, these findings are novel and might constitute the base for further understanding this condition.

However, such results should be interpreted with caution. Because of the multiple comparison performed, there is always the possibility that these results might be due to chance. Furthermore, this analysis is exploratory as the two groups had very different sizes. Finally, these findings apply to the FCD patients who participated in this study and would be more valuable if they could be replicated in the future with a bigger size sample.

3.6.2 Normative data

When looking at the cognitive outcome measures of the DECODE participants in comparison to the normative scores, it is easy to conclude that people who took part in the study do not differ from the

average general population. Both people with SCD and FCD performed very closely to the average in the measurements of mental flexibility, task switching, attention and verbal fluency. However, all participants' T-scores on the RAVLT test, were below 50. The RAVLT test is used to measure learning, recognition, immediate memory span and susceptibility to interference (Sullivan & Bowden, 1997). A study conducted by Tierney et al. (1996), examined people who showed symptoms of memory impairment in the last 3 months but, were nondemented. This study showed that RAVLT has important value when predicting who of these people were more likely to develop dementia in the next 2 years (Tierney et al., 1996). Another study replicated such results in a sample of people with SCD, by identifying the group of people who would develop AD in the next years (Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, & Garcia-Sanchez, 2003). Consequently, it can be suggested that RAVLT could possibly help researchers identify early people with SCD and FCD who are at higher risk of AD. Such hypothesis could be examined in the future by longitudinal studies.

In addition to that, after comparing the MoCA scores of both the SCD and FCD groups with the normative data, it is easy to observe that the means are quite close. Neither the SCD nor the FCD people are far from the normative data of a healthy sample so, one can conclude that they performed within the expected normal range. This verifies that indeed people who present with memory complaints at this stage, do not show any evidence of cognitive impairment on objective tests.

Similarly, the DASS scores of the participants were very close to the scores of healthy populations, indicating that the people with SCD and FCD who participated in this study did not have elevated levels of depression, anxiety or stress.

This section discussed only some of the assessments as unfortunately, there are not normative data available for all the cognitive tests and psychological questionnaires that participants were administered. The comparisons showed that both SCD and FCD groups scored lower on the RAVLT test than the rest of cognitive measures. This finding is in accordance with previous studies suggesting that RAVLT has good predictive value when identifying people with memory problems who might progress to AD (Estevez-Gonzalez et al., 2003).

Regarding the rest of the cognitive tests, people who participated in the DECODE study did not show any significant cognitive impairment and were not likely to have high depression, anxiety and stress levels. Their similarity to the general population makes it hard for researchers and clinicians to identify and further understand these populations. These findings could contribute to the effort of describing and investigating the diverse groups of SCD and FCD people. Ultimately, this will enable researchers to develop new and sensitive tools that will allow their identification at the earliest stage possible.

3.6.3 Cognitive Neuropsychology outcome measures

Regarding the cognitive tests, the one that seems to differentiate the two groups is the TOMM, which is a performance validity test (PVT). PVTs are cognitive tests that are easily passed by most people,

even those who demonstrate brain damage. They are used to provide a measure of the degree to which a person provided enough effort and produced valid cognitive test results (Lippa, 2018).

The TOMM cut-off that is normally used in the clinical setting is 45 as a score above that level indicates credible performance. The complete administration is consisting of two learning trials. Previous studies have shown that passing Trial 1 can predict the performance on the following trial (O'Bryant et al., 2008). This study found that FCD patients were more likely to fail Trial 1 of the TOMM test, than SCD participants. This suggests that TOMM failure might be an early sign of FCD.

3.6.4 Psychological variables and Lifestyle questionnaires

When comparing the FCD and SCD participants' performance on the psychological questionnaires, I observed that the FCD patients had a higher score on the Non React factor of the Five Facet Mindfulness questionnaire. This factor refers to the ability of people to realise their thoughts and emotions but, at the same time let them go without getting caught up in them (Baer et al., 2008). The relationship between mindfulness and FCD has not been explored in the past but, one possible explanation for this difference could be the fact that FCD patients were more likely to meditate, than SCD participants. For this reason, they could probably have been better trained to adopt this skill.

This chapter examined the relationship between SCD and FCD participants in the DECODE study. There were some significant differences that need to be interpreted with caution, due to the problem of multiple comparisons.

There may be a scope for developing a test to identify people at risk of FCD. This would benefit patient care and identifying patients for research but, more research is warranted in this area.

Chapter 4 Interventions for people with Subjective Cognitive Decline

In this chapter I will discuss some of the hypotheses we tested in the randomised controlled trial DECODE (Development and Evaluation of Interventions in People with Subjective Cognitive Decline). The aim of this project was to test the effectiveness of two different non-pharmacological interventions on the cognition and psychological well-being of people with Subjective Cognitive Decline (SCD). The two interventions discussed here are a Mindfulness meditation course and a course about Lifestyle factors which was conducted for the purposes of this study.

4.1 Introduction

4.1.1 Mindfulness meditation

As discussed previously, the central element of mindfulness meditation is to pay attention to the present moment by focusing on thoughts, emotions and bodily sensations in an open and non-judgemental way (Detert, 2015). Clinical interventions based on mindfulness training are becoming more and more popular (Baer, 2003).

The most popular approach is the Mindfulness-Based Stress Reduction (MBSR) which was developed and brought into health care in the 1980s by Jon Kabat-Zinn (Kabat-Zinn, 1982). The combination of MBSR with elements of cognitive-behavioural therapy (CBT) has led to what is known as Mindfulness-Based Cognitive Therapy (MBCT) which was shown to be an efficient intervention in preventing depression relapses (Teasdale et al., 2000). MBSR involves training through practices like mindful eating and walking, yoga, sitting meditation and the body-scan.

The literature on the effects of mindfulness interventions suggests that they can help reduce psychological symptoms such as anxiety, stress and depression and help treat pain and eating disorders (Kabat-Zinn, 1982; Kabat-Zinn et al., 1992; Kristeller & Hallett, 1999; Shapiro et al., 1998; Teasdale et al., 2000).

Moreover, even short-term training in mindfulness has been shown to improve cognitive flexibility and performance on attention tasks (Moore & Malinowski, 2009; Zeidan et al., 2010).

Despite its popularity, the way in which mindfulness meditation improves physical and psychological well-being is not yet fully understood (K. W. Brown, Ryan, & Creswell, 2007). Moreover, along with several methodological limitations in mindfulness studies, its effectiveness has not yet been conclusively established (Baer, 2003).

One of the purposes of this study was to examine whether mindfulness meditation training could promote and maintain optimum cognitive function and psychological well-being in people with SCD.

People with SCD do not have any diagnosis of cognitive impairment and experience a subjective worsening of their memory and thinking abilities. The uncertain period between experiencing SCD and receiving a diagnosis of dementia, or being reassured that there is no dementia, can be long and distressing. However, there is little to be offered to this population in terms of support and treatment. In this study we examined if mindfulness training would enhance cognitive function and psychological factors in people with SCD, when compared to a lifestyle intervention and a control group.

Following the development of new technologies, it seemed to us like an intervention that is delivered online has many advantages over a face-to-face course. Firstly, it is easily accessible, and people can complete it from the comfort of their environment without having to travel to a certain location. In addition to that, an online intervention is available 24/7 and can be accessed, revisited and completed at each participant's convenience allowing them to work at their own pace. And lastly, it is cost effective as it is cheaper than a face-to-face course with an instructor.

For the first intervention (mindfulness training) I chose an already commercially available course called "Be Mindful Online" (www.bemindfulonline.com). This course is delivered online and has been developed to cover the core elements of Mindfulness-Based Cognitive Therapy (MBCT) and Mindfulness-Based Stress Reduction (MBSR). It is a 4-week programme where participants are offered audio and video files and do not have any personal contact with the instructors. Exercises include the "body scan", which instructs people to move their attention through different parts of the body for 40 minutes. Other practices are mindful eating, simple stretches, breathing and noticing sensations, emotions and thoughts. The emphasis of this course is on observing the thoughts and their effects on mood. Through psycho-education and experiential exercises, the aim is to attend to sensory and mental aspects of our experiences and accept them in a non-judgmental way.

The effectiveness of this course has been described in a study conducted by the Department of Psychiatry in Oxford University, where participants who completed the course reported 58% reduction in anxiety, 40% in stress and 57% in depression levels (Krusche, Cyhlarova, & Williams, 2013). Moreover, in another study by the same department researchers found that people who completed the course presented with 40% reduction in perceived stress (A. Krusche, E. Cyhlarova, S. King, & J. M. Williams, 2012).

4.1.2 Lifestyle factors intervention

The idea behind the second intervention (lifestyle factors course) was to offer participants evidence from the current literature regarding modifiable lifestyle factors that could possibly promote and maintain optimum cognitive function. Besides the information given, I also wanted to provide direct advice and ideas of how to incorporate what has been suggested into their everyday life and eventually follow a healthier lifestyle.

As shown in a prospective cohort study which was set up in Caerphilly in 1979 and aimed to investigate the effect of environmental factors on chronic disease (Elwood et al., 1999a), people who engage in physical and social activities, avoid the excessive use of alcohol, do not smoke and also review their health, can reduce their risk of dementia by up to 60%. A different study conducted in Finland and known as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) suggested that a multidomain intervention which targets modifiable vascular and lifestyle factors like diet, exercise and cognitive training, can help people at-risk to preserve and even improve their cognitive function (Tiia Ngandu et al., 2015). What is also very interesting about the FINGER study is that researchers focused on people who were at predementia and presymptomatic stages, when an intervention might be most effective.

It seemed that the best way to discuss such findings would be to create an online platform that would include evidence from previous studies and at the same time encourage people to make a positive change and live a healthier lifestyle by controlling the modifiable factors that could potentially promote brain health. Besides the literature, I researched other relevant sources that aim to promote brain health. One example is the "Hello Brain" website (http://hellobrain.eu/en/). This website provides easy-to-understand scientific information on how our brain works and what we can do to keep it healthy. It includes video presentations and expands on five top tips that could promote brain health (get physically active, stay socially engaged, challenge your brain, manage stress and adapt your lifestyle to protect your brain). It has been funded by the European Union's Seventh Framework Programme for research, technological development and demonstration and is freely accessible. Another source I consulted while putting the intervention together is the book "The Sharp Brains guide to brain fitness: How to optimize brain health and performance at any age" (Fernandez, 2013). This book features an analysis of several scientific studies conducted in the past decade as well as interviews with experts who give their insight regarding brain health thinking. In addition to that, the Sharp Brains works as a guidance for people to identify their individual needs and integrate the relevant lifestyle changes. Lastly, I took inspiration from the "6-steps leaflet for reducing dementia risk", produced by Professor Antony Bayer and the Wales Government. The main characteristic that all these sources had in common was the intention to raise awareness on the impact that lifestyle choices can have on our brain health and the guidance they provide towards making a positive change.

I wanted both the Mindfulness and Lifestyle interventions to have the same duration, so the Lifestyle factors course was delivered online for the duration of 4 weeks. I named it "The 4 Week Change Challenge" and invited participants to watch one video presentation each week and try and follow the advice given. Besides the informative/encouraging style of the course, there was one main task that we asked participants to carry out for the whole duration of the course. This task was a 15-minute brisk walk, 3 times a week and was introduced to them at the first week of the course, when physical activity

was discussed. Week 2 was about diet and related factors like drinking habits, sleep behaviour and smoking, Week 3 involved mental stimulation and Week 4 was about social interaction.

4.2 Hypotheses

As discussed previously, the first hypothesis of this study is that the Mindfulness meditation course will improve psychological factors and cognitive function in people with SCD. The second hypothesis is that the Lifestyle factors intervention will improve psychological factors and cognition in people with SCD. Our scope was to compare these two interventions against each other and against a control group, in order to evaluate their effectiveness.

4.3 Participants

This chapter discusses interventions only for people with SCD. Regarding the recruitment methods, most SCD participants have self-reported themselves by responding to our advertising (n=65) which included the Bristol Post Weekend magazine, local newspapers and libraries and the BRACE charity newsletter and website. In addition to that, other recruitment pathways included the ReMemBr group's healthy volunteer database (n=15) and the Join Dementia Research service (n=4). Finally, people were recruited through other participants who spread the word (n=5) and 1 participant was referred through a Neurologist in our clinic. Some of the participants' demographic data can be found below in Table 4.1. Table 4.2 depicts participants' scores on cognitive tests per group, at baseline and Table 4.3 depicts participants' scores on psychological questionnaires per group, at baseline.

Table 4.1 Demographic data for all SCD participants at baseline (per group)

Variable	**Mindfulness** N= 30		**Lifestyle** N= 29		**Control** N= 31	
	Mean (Min-Max)	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**
Age in years (range)	63.47 (45-80)	9.24	61.55 (48-75)	8.13	64.10 (45-89)	10.15
Education in years (range)	14.98 (6-24)	3.95	15.31 (8-24)	4.23	15.58 (10-24)	3.79
Gender (M/F)	6/24 (20%/80%)		12/17 (41.4%/58.6%)		10/21 (32.3%/67.7%)	
Work status (Working/Retired/Currently not working)	14/16/0 (46.7%/53.3%/ 0%)		16/12/1 (55.2%/41.4%/ 3.4%)		16/13/2 (51.6%/41.9%/ 6.5%)	
Area (Urban/Suburban/Rural)	11/11/8 (36.7%/36.7%/ 26.7%)		11/11/7 (37.9%/37.9%/ 24.1%)		14/15/2 (45.2%/48.4%/ 6.5%)	
People they live with	1.03 (0-3)	0.89	1.14 (0-5)	0.95	1.19 (0-4)	1.01
Smoking (Smoker/Ex-smoker/Never smoked)	0/13/17 (0%/43.3%/ 56.7%)		1/7/21 (3.4%/24.1% 72.4%)		1/10/20 (3.2%/32.3%/ 64.5%)	
Alcohol units (per week)	7.38 (0-56)	11.52	8.26 (0-22)	7.22	9.48 (0-60)	14.35
Exercise (Y/N)	27/3 (90%/10%)		23/6 (79.3%/20.7%)		22/9 (71%/29%)	
Meditation (Y/N)	2/28 (6.7%/93.3%)		0/29 (0%/100%)		1/30 (3.2%/96.8%)	
BMI Interpretation (Healthy/Overweight/Obese/ Missing)	15/11/4/0 (50%/36.7%/ 13.3%/0%)		11/12/5/1 (37.9%/41.4%/ 17.2%/3.4%)		11/12/8 (35.5%/38.7%/ 25.8%)	
Sought help before (Y/N)	6/24 (20%/80%)		7/22 (24.1%/75.9%)		4/27 (12.9%/87.1%)	
GP visits (past year)	2.80 (0-8)	2.19	2.72 (0-12)	2.66	2.84 (0-12)	2.56
Blood pressure (Y/N)	5/25 (16.7%/83.3%)		4/25 (13.8%/86.2%)		8/23 (25.8%/74.2%)	
Cholesterol (Y/N/Don't know)	9/20/1 (30%/66.7%/ 3.3%)		11/18/0 (37.9%/62.1%/ 0%)		7/23/1 (22.6%/74.2%/ 3.2%)	

Table 4.1 Demographic data for all SCD participants at baseline (per group; continued)

Variable	**Mindfulness** N= 30		**Lifestyle** N= 29		**Control** N= 31	
	Mean (Min-Max)	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**
Diabetes (Y/N)	3/27 (10%/90%)		4/25 (13.8%/86.2%)		0/31 (0%/100%)	
Stroke (Y/N)	0/30 (0%/100%)		0/29 (0%/100%)		0/31 (0%/100%)	
TIA (Y/N)	0/30 (0%/100%)		0/29 (0%/100%)		0/31 (0%/100%)	
Heart disease (Y/N)	3/27 (10%/90%)		1/28 (3.4%/96.6%)		4/27 (12.9%/87.1%)	
Depression history (Y/N/Don't know)	12/18/0 (40%/60%/0%)		13/16/0 (44.8%/55.2%/ 0%)		11/19/1 (35.5%/61.3%/ 3.2%)	
Anxiety history (Y/N)	8/22 (26.7%/73.3%)		7/22 (24.1%/75.9%)		7/24 (22.6%/77.4%)	
Family history of AD/dementia (Y/N/Don't know)	17/12/1 (56.7%/40%/ 3.3%)		19/10/0 (65.5%/34.5%/ 0%)		12/18/1 (38.7%/58.1%/ 3.2%)	
Psychiatric condition (Y/N)	0/30 (0%/100%)		5/24 (17.2%/82.8%)		1/30 (3.2%/69.8%)	
Neurological condition (Y/N)	1/29 (3.3%/96.7%)		2/27 (6.9%/93.1%)		2/29 (6.5%/93.5%)	
Handedness (R/L)	23/7 (76.7%/23.3%)		23/6 (79.3%/20.7%)		25/6 (80.6%/19.4%)	

Table 4.2 Scores on cognitive tests for all SCD participants at baseline (per group)

Variable	**Mindfulness** N= 30		**Lifestyle** N= 29		**Control** N= 31	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
CRI_q Total	131.67	16.81	133.34	15.04	133.13	19.9
MOCA	27.17	2.14	27.28	2.10	27.42	2.01
TOMM (Trial 1)	48.83	2.14	48.86	1.46	48.71	1.66
RAVLT Total	42.83	8.85	43.59	8.03	42.93	11.74
RAVLT LD	8.10	3.28	8.76	2.79	8.48	3.92
Trail A	31.80	11.99	26.07	7.35	28.87	7.93
Trail B	73.23	31.99	68.61	27.60	71.60	31.45
Letter fluency	40.20	8.65	40.86	8.32	40.71	10.79
Semantic fluency	20.73	5.51	22.79	5.15	21.45	4.84
N1 reaction time	586.52	173.35	545.97	105.43	570.11	164.29
N2 reaction time	737.11	148.62	747.01	184.15	765.49	137.65
N3 reaction time	813.64	178.17	806.67	199.21	807.50	179.49

CRI_q= Cognitive Reserve Index questionnaire, MOCA= Montreal Cognitive Assessment, TOMM= Test of Memory Malingering, RAVLT= Rey Auditory Verbal Learning Test, N reaction time= N-back test for trials 1, 2 and 3

Table 4.3 Scores on psychological questionnaires for all SCD participants at baseline (per group)

Variable	**Mindfulness** N= 30		**Lifestyle** N= 29		**Control** N= 31	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
HAI Total	14.57	5.46	13.52	6.25	12.74	6.03
FFMQ Observe	27.30	5.93	24.76	5.67	24.68	5.28
FFMQ Describe	27.93	6.83	26.24	6.45	27.45	6.59
FFMQ Act with awareness	24.87	5.87	23.52	3.81	24.16	6.72
FFMQ Non judge	28.07	5.26	28.38	6.98	27.77	6.04
FFMQ Non react	21.33	4.94	20.55	4.87	21.19	5.31
FMDQ Total	6.30	1.90	6.38	2.30	6.10	2.48
DASS Depression	5.53	5.32	8.97	11.00	7.73	9.08
DASS Anxiety	4.20	3.42	5.76	8.48	5.33	6.27
DASS Stress	11.00	6.74	12.17	7.94	11.27	9.75
DASS Total	20.73	11.51	26.90	23.26	24.33	22.53
WHO	14.20	4.60	15.31	4.68	14.48	5.05

HAI= Health Anxiety Inventory, FFMQ= Five Facet Mindfulness Questionnaire (Five Facets: Observe, Describe, Act with awareness, Non judge, Non react), FMDQ= Functional Memory Disorder Questionnaire, DASS= Depression, Anxiety and Stress scale, WHO= WHO-5 Well-being questionnaire

As described above in General Methods, the sample consisted of 90 people with SCD. All of them were ≥ 45 years old and responded positively to the question "Are you concerned or worried that you are experiencing significant decline in your thinking abilities, more than just normal ageing?". None of the participants had any diagnosis of dementia, any neurological or psychiatric disorder. Moreover, no one knew their ApoE genotype and had not been exposed to any of the tests within the past three months. Due to the random group allocation I wanted to make sure that everyone would be eligible for all groups. Since the lifestyle factors course involved the exercise of doing a brisk walk for 15 minutes, three times per week, I went through the Fitness Australia Adult Pre-Exercise Screening questionnaire with all participants during the screening call. Every participant passed the test indicating there was low health risk for undertaking this task. See Figure 3.1 for participant flow from recruitment to follow-up (CONSORT Flow diagram).

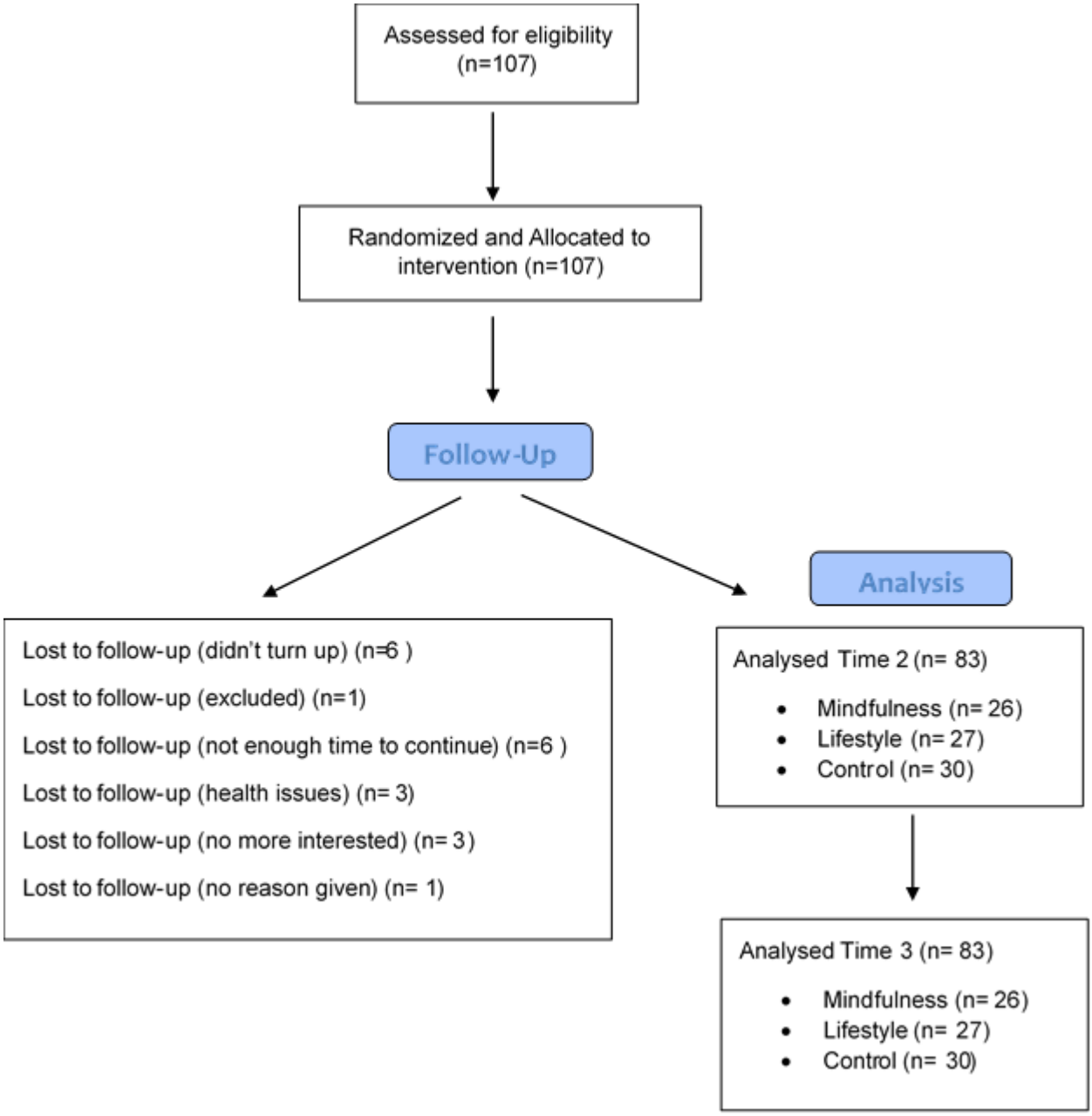

Figure 4.1 CONSORT Flow Diagram

4.4 Tasks and procedure

At first, the baseline visit lasted around 1 ½ hours. All visits took place at the Brain Centre in Southmead hospital, North Bristol NHS Trust. Upon their arrival, participants were offered a drink and they were asked to read the Participant Information sheet. Afterwards, they had the time to ask any questions and they were given the Consent form to sign. They were again asked the screening question "Are you concerned or worried that you are experiencing significant decline in your thinking abilities, more than just normal ageing?" (Smart et al., 2014). Following a positive response, they completed the Background information questionnaire (see Appendix) which included demographic questions as well

as questions about health concerns and past medical history. Next, they completed a cognitive test battery, which included the following assessments: Montreal Cognitive assessment (MoCA) (Nasreddine et al., 2005), Test of Memory Malingering (TOMM) (Tombaugh, 1997), Cognitive Reserve Index (CRIq) (Nucci et al., 2012), Letter Verbal Fluency (Gladsjo et al., 1999), Semantic Category Fluency (Gladsjo et al., 1999), Rey Auditory Verbal Learning Test (RAVLT) (Geffen et al., 1994; Lezak, 1976, 1983; Majdan et al., 1996), N-back test (Verhaeghen & Basak, 2005) and Trail Making test parts A and B (Reitan, 1955). At the two follow-up visits, they repeated all the cognitive test with the exception of MoCA, TOMM and CRIq.

Finally, participants were asked to fill in the following questionnaires: Health Anxiety Inventory (HAI) (Salkovskis et al., 2002), Five Facets Mindfulness Questionnaire (Baer et al., 2006), Readiness to change questionnaire (Prochaska et al., 1994), Depression Anxiety and Stress Scale-21 items version (DASS) (Henry & Crawford, 2005) and WHO-Five well-being Index (WHO-5) (Bech et al., 2003). These questionnaires were repeated at the two follow-up visits.

All tests and questionnaires were completed individually with an examiner and the results were not disclosed to the participants, unless they raised a concern. This happened in one occasion and following the procedure stated in the protocol, the participant was invited for an appointment with the Clinical Neuropsychologist Dr Margaret Newson who discussed the results with them, advised them further and informed their GP. The participant was consequently removed from the study.

Following the completion of the baseline tests and questionnaires, each participant was randomly assigned to one of three groups (Mindfulness meditation, Lifestyle factors, Control) and was also given two sets of Diaries. The randomisation envelope included their group assignment and the appropriate instructions to follow. It was explained to them that they should open the envelope after the end of the session. No matter what group they had been assigned to, the guidelines were instructing all participants to fill in the first set of Diaries for 1 week, then attend the intervention that lasted for 4 weeks (the Control group was advised to wait for 4 weeks) and finally, fill in the second set of Diaries before coming in for their second visit. The Diaries constituted a tool to document everyday activities such as sleep, eating and drinking habits, exercise, meditation, alcohol use, smoking, mental stimulation and social interaction. Each set of Diaries consisted of 7 leaflets (one for each day-see Appendix).

The second visit (first follow-up) took place at least 6 weeks after the first one and the third visit (second follow-up) took place 6 months after the second. Both follow-up visits lasted approximately 1 hour.

Finally, the study involved a one-off optional blood sample to identify the participants' ApoE genotype. The samples were obtained either on the second or third visit depending on participant's preference. Results are presented in Chapter 6.

4.5 Data analysis

Analyses of variance were performed with time as the within subject variable and group assignment as the between subject variable. All data were analysed using IBM SPSS Statistics 24 software.

4.6 Results

4.6.1 Mindfulness meditation/Lifestyle factors intervention and Cognitive function

Analyses of variance showed that there was no group effect on the RAVLT total correct immediate recall $F(2,4)= .522$, $p= .720$ and no group effect on RAVLT short delay over time $F(2,4)= .952$, $p= .435$ (Figure 4.2 and Figure 4.3).

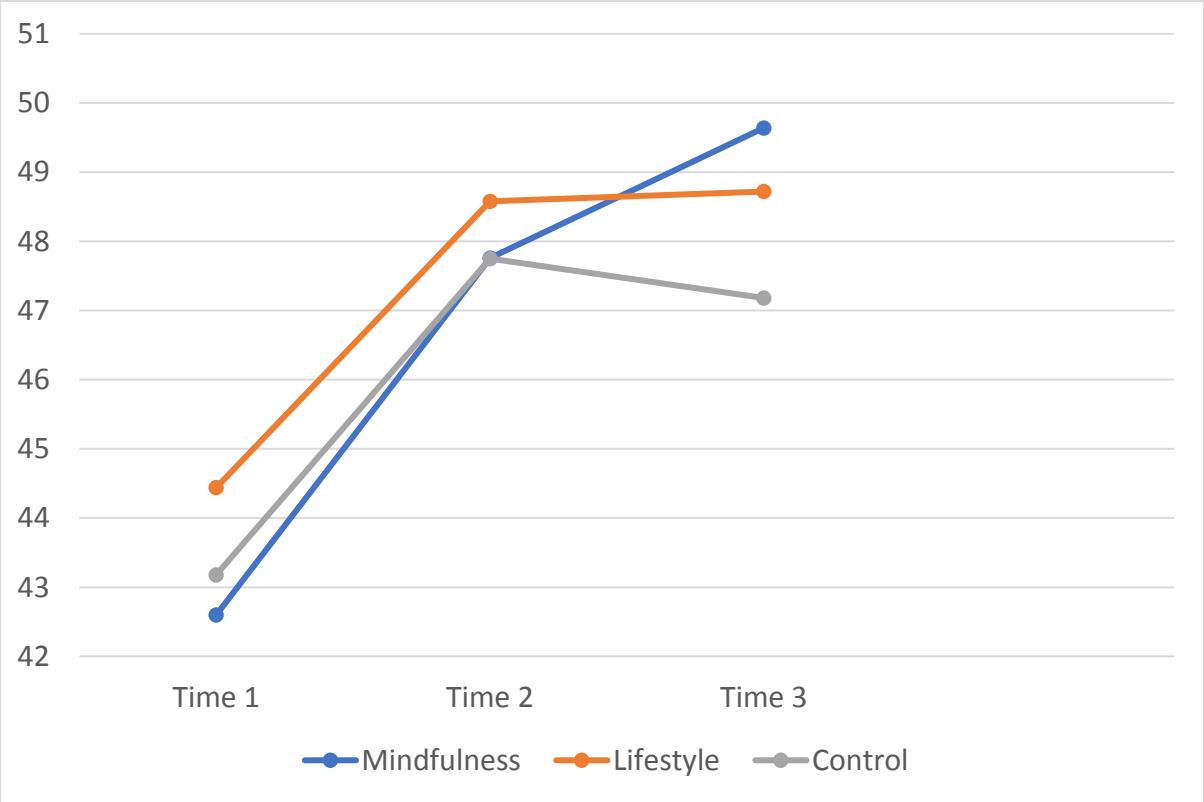

Figure 4.2 Total number of correct words recalled at all immediate recall trials on RAVLT

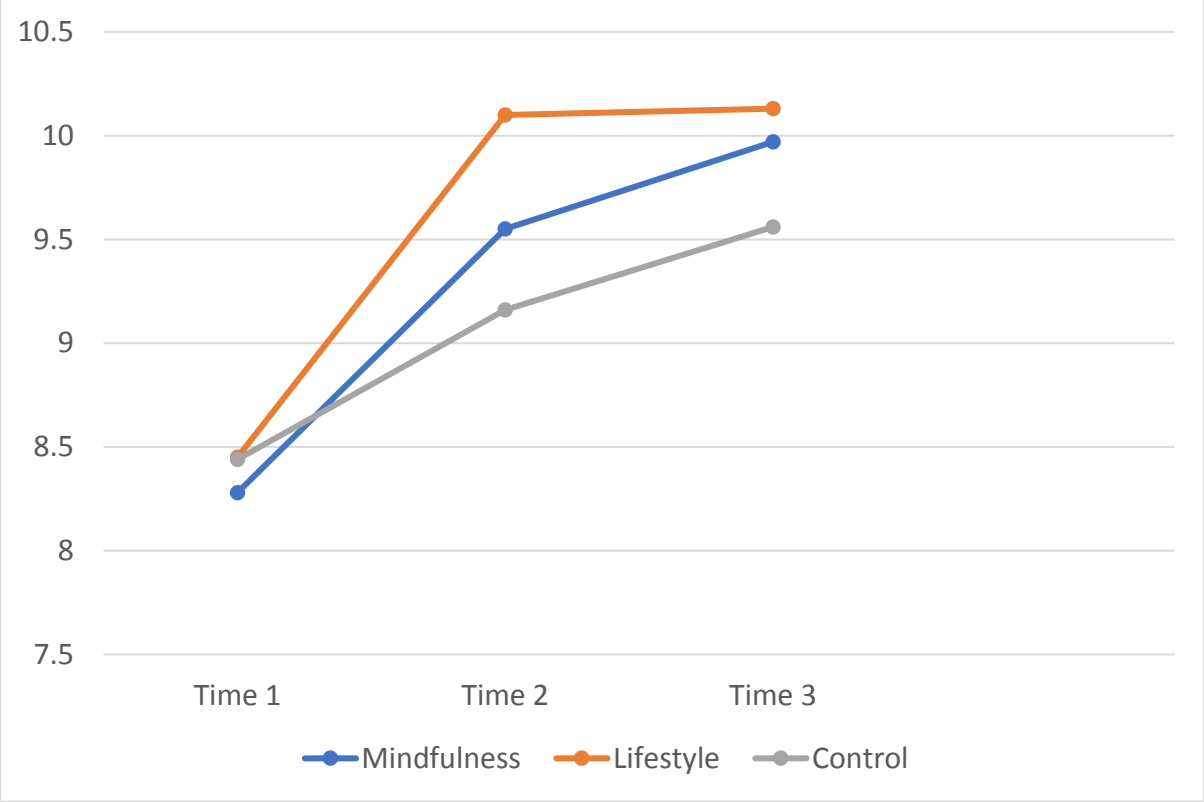

Figure 4.3 Total number of correct words recalled on RAVLT short delay

There was no effect of group over time on RAVT long delay trial $F(2,4)= 2.141$, $p= .078$ (Figure 4.4). For this trial we asked participants to recall as many words as possible out of the first list (15 words) 20 minutes after the first trial.

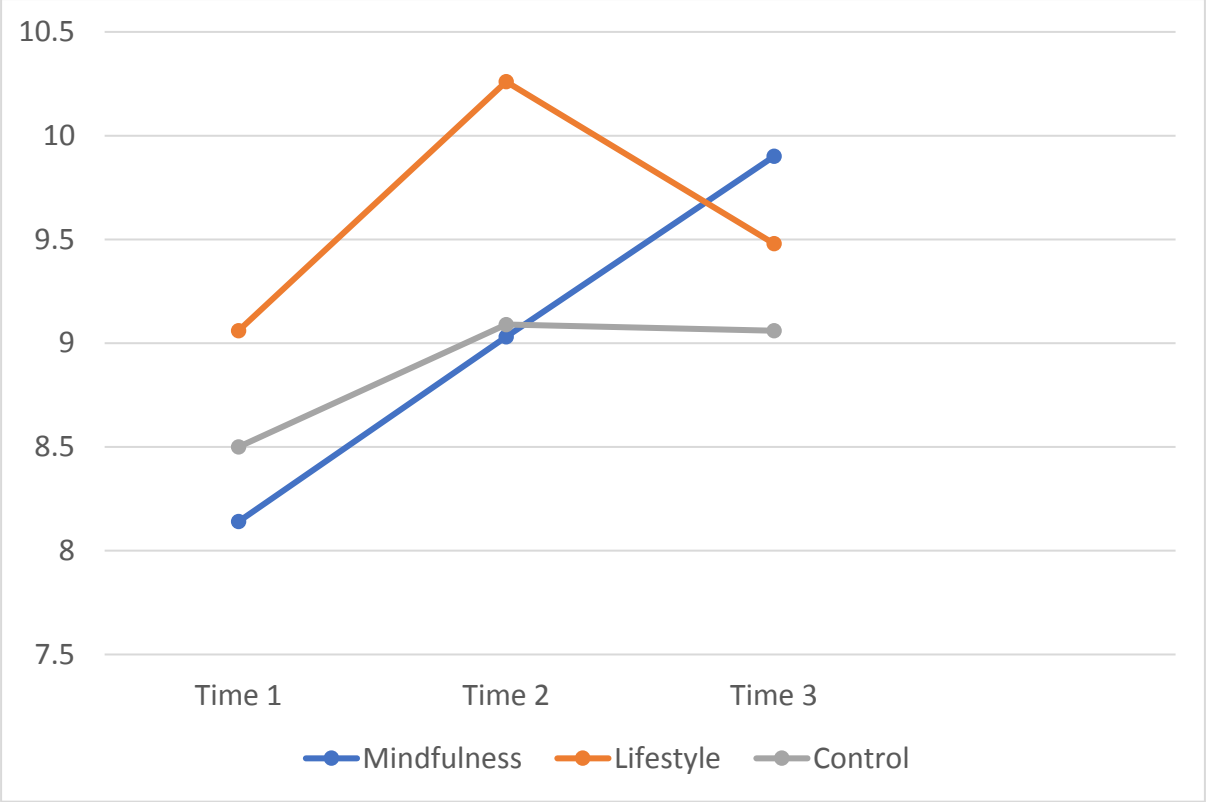

Figure 4.4 Total number of correct words recalled on RAVLT long delay (20 minutes) over time

Regarding the rest of the cognitive outcome measures (Trail Making, Letter fluency, Semantic fluency, N-back test) no effect of group was observed over time (not sure if I should insert Figures for all the tests).

4.6.2 Mindfulness meditation/Lifestyle factors intervention and Psychological factors

As far as Psychological assessment is concerned, similarly to the cognitive outcome measures above, there was no significant effect of group over time for almost none of the questionnaires.

The only exception was the WHO-5 well-being questionnaire. A repeated measures ANOVA revealed a significant group by time interaction $F(2,81)= 4.732$, $p< .05$, $\eta^2 = .105$ (Figure 4.5) showing that from all three groups, people in the Mindfulness group scored higher on the well-being scale at the 6-week follow-up compared to baseline. However, such effect was not maintained at the 6-months follow up $(2,81)= 2.588$, $p= .081$ (Figure 4.6).

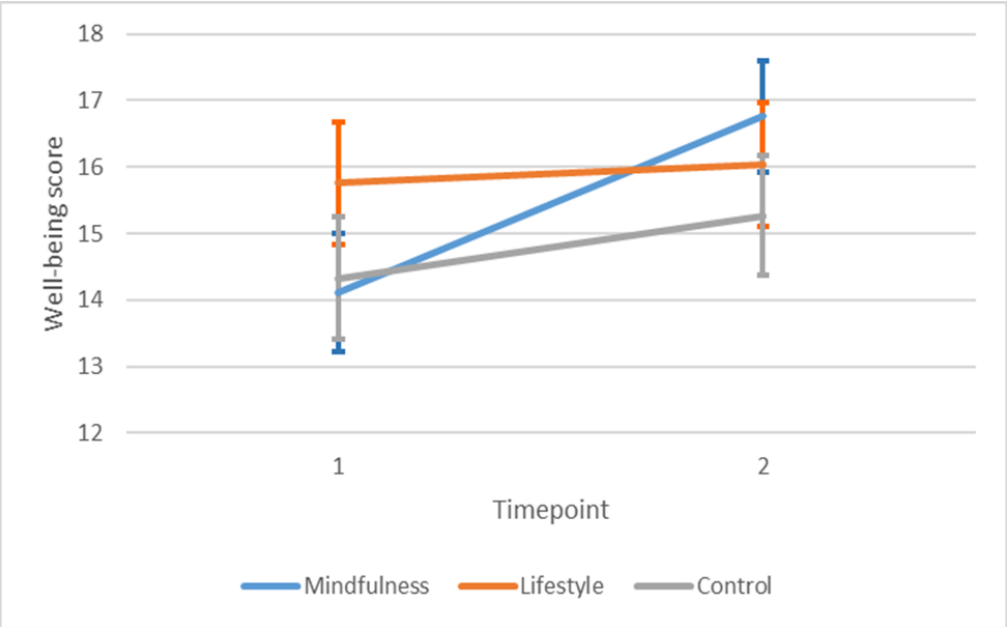

Figure 4.5 WHO-5 well-being scores for all three group before and after intervention (or 6 weeks for the Control group). Error bars represent the standard error of the mean.

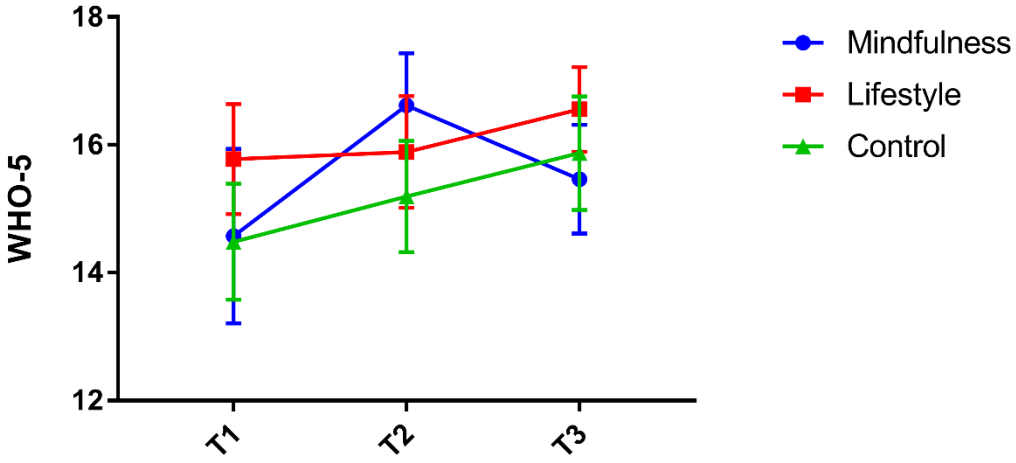

Figure 4.6 WHO-5 well-being scores for all three group at three timepoints (baseline, 1st follow-up/6 weeks and 2nd follow-up/6 months). Error bars represent the standard error of the mean.

4.7 Discussion

4.7.1 Mindfulness meditation/Lifestyle factors intervention and Cognitive function

Contrary to what expected, neither of these courses improved significantly the cognitive function of the sample.

This could be due to various reasons. First, I must examine the sample's characteristics as this might not be representative of the general population. People with SCD constitute a very diverse group and particularly in this occasion, where the majority of participants were recruited through advertisements, it is very possible that variables like education or exercise level were already high. This could be possibly because some participants were already aware of the existing evidence regarding modifiable lifestyle factors that might promote brain health and were very active to begin with (both physically and mentally).

Another reason could be the participants' compliance with the interventions. This project required some sort of commitment and continuity for approximately 8 months, so it is very likely that some individuals stopped practicing or were not practicing with the pace that would make an intervention most effective.

A third explanation for the absence of an effect could be the nature and the duration of the interventions. Similar studies that asked participants to practice Mindfulness, had different structure (face to face with an instructor rather than online) and different duration (at least 6 weeks-reference). However, an established online course was chosen, especially one that had had already been used in research projects where participants reported significantly lower levels of stress, anxiety and depression after completing it (A. Krusche, E. Cyhlarova, S. King, & J. M. G. Williams, 2012).

Finally, as mentioned earlier, the SCD population has not yet fully been described as it is very diverse. At this basis, one of the hypotheses is that a subgroup of such population could be experiencing memory concerns due to psychological factors such as depression or anxiety. I would expect this group to be benefited from practicing relaxation techniques taught through Mindfulness but, this would not necessarily be the case for people whose concerns might have a biological basis and are related to early neurodegenerative disease.

4.7.2 Mindfulness meditation/Lifestyle factors intervention and Psychological factors

The observations regarding the effect of the interventions on psychological outcome measures were like the ones described above for the cognitive tests. The only exception in this category was the WHO-5 which was used to measure the well-being of participants. This is a self-report questionnaire which constitutes of 5 items and invites participants to rate certain statements depending on how often they applied to them. Participants completed this questionnaire at all three visits, and it was found that people

in the Mindfulness group improved more than the Lifestyle and Control groups between the first and second visit. This means that compared to baseline, people in the Mindfulness group reported higher levels of well-being immediately after completing the course. This finding supports the link between Mindfulness and well-being beyond the general population to people with SCD. However, such an effect was not maintained at the third visit (6-months follow-up). This could be possibly because participants didn't practice as much after the end of the course.

To conclude with, these findings suggest that Mindfulness training may be an effective low-cost intervention to help improve the well-being of people with SCD. It is very important to consider though, that Mindfulness is not just about attending a course, but rather practising regularly and turning this into a way of living. Consequently, such results might only refer to a short-term effect after the completion of Mindfulness training. These findings would be more meaningful if they could be replicated with a larger sample of SCD participants.

Chapter 5 Readiness to change as a predictor of change in behaviour of people with Subjective Cognitive Decline

The aim of this chapter is to describe the effect of readiness to change on the behaviour of the sample. Specifically, I want to examine if people in the lifestyle intervention group who stated that they were willing to change, will show any changes in the amount of exercise they do on a weekly basis. The scope thus, is to investigate the relationship between readiness to change and actual change, or the absence thereof.

5.1 Introduction

Change is an inevitable part of our everyday lives. Most of the changes that occur in the world and in ourselves are beyond our control. However, in some cases we might be able to have some power over intentional changes in our thoughts, feelings and behaviour (Prochaska et al., 1994). In this study I do not discuss change from a philosophical perspective but, rather from the aspect self-change in behaviour as it described by Prochaska and DiClemente in their Transtheoretical Model (Prochaska et al., 1994).

5.1.1 Transtheoretical Model

The Transtheoretical Model was created to describe the road towards changing a problematic behaviour or overcoming addiction. According to this model, change can occur in six stages and knowing your stage is the key to success. The six stages are: Precontemplation, Contemplation, Preparation, Action, Maintenance and Termination (Prochaska et al., 1994)

Precontemplation refers to the point when the person is not even aware of the problem. They might be nagged by their close ones to act on it, but they are cannot see it. Contemplation describes the stage in which a person acknowledges that there is an issue and thinks about changing it but might not be ready to do it yet. The next step, Preparation is when someone is ready to switch their behaviour within the next month. Action describes the actual move, taking the new step that the person has been preparing for. Maintenance is the effort to sustain the new behaviour and solidify the gains. During this stage the individual is also trying to prevent potential relapse. Lastly, Termination is when people achieve the final goal and can exit the spiral of change (Prochaska et al., 1994).

Prochaska et al. (1994) suggested that it is really important to know in which of the above stages a person is, in order to predict whether they will succeed in their attempt to change, or not. This can be assessed by responding to the statements that have been described by the same researchers (1994). Based on these four statements, I created the "Readiness to change" questionnaire which is described later in this chapter.

5.2 Hypothesis

Participants in the Lifestyle group were given the task of doing a 15-minute brisk walk, at least three times a week for 4 weeks, that was the duration of the course. In addition to that, all participants were given three sets of diaries to complete at baseline, right after their course and six months later. These diaries were questionnaires to monitor some of their everyday habits, one of which was exercise and brisk walking.

The hypothesis in this chapter is that people from the Lifestyle group who indicated that they were ready to change (contemplation and preparation stage), will show an increase in the amount of exercise they performed.

5.3 Tasks and procedure

As described in the General Methods section, all participants were administered the "Readiness to Change" questionnaire, as part of the assessment conducted in all three visits. This is a short questionnaire I put together for the purposes of this study, based on the Transtheoretical Model of Change (Prochaska et al., 1994). It consists of four questions: "Do you exercise?", "In the past year, have you made a change to your level of exercise?", "Do you meditate?" and "In the past year, have you made a change to your meditation practice?". For the questions "Do you exercise?" and "Do you meditate?" the answer was either "Yes" or "No" whereas, for the other two questions had the possible answers: a. "More than 6 months ago", b. "Less than 6 months ago", c. "I am intending to change in the next month", d. "I am intending to change in the next 6 months", e. "I am not intending to change".

This questionnaire was administered at all three visits (baseline, post-intervention and 6 months) but, I eventually only used the baseline responses to see where everyone was standing when they entered the study. Moreover, in order to examine the hypothesis I took into consideration only the first part of our Readiness to Change questionnaire, which referred to exercise: "Do you exercise?" and "In the past year, have you made a change to your level of exercise?".

Participants who responded c. "I am intending to change in the next month" and d. "I am intending to change in the next 6 months" were considered to be at the contemplation and preparation stage and were included in the "Changers" group. This group was compared against the "No-changers" group which included the participants who responded e. "I am not intending to change".

5.4 Participants

As mentioned above, for the purposes of this chapter I was only interested in people who stated that they were either intending to change in the next 1 or 6 months, or not intending to change at all. Consequently, participants who answered a. “More than 6 months ago” and b. “Less than six months ago” on the baseline Readiness to Change questionnaire were excluded (N= 42). Additionally, I also excluded 5 people who had not reported their brisk walk minutes for the three timepoints. Finally, 53 people were included in the analysis. In more detail, the sample consisted of 48 people with Subjective Cognitive Decline (SCD) and 5 people with Functional Cognitive Disorder (FCD), who are considered to constitute a subgroup of SCD, hence they have been included in the analysis.

5.5 Results

5.5.1 Demographic data

Data for demographic variables were normally distributed so, the statistical analysis performed was independent sample t-tests for numerical variables and chi-square for the one categorical variable (Age). The results showed that No-changers had a significantly higher Body Mass Index than Changers. All other comparisons were non-significant, and participants’ demographic details are presented in Table 5.1.

Table 5.1 Characteristics of Changers versus Non-changers

	Changers N= 37 Mean (Std. Dev)	**No-changers** N= 16 Mean (Std. Dev)	t-test/ x^2	Sig. (p)
Age	62.95 (8.66)	64.75 (11.54)	t (56)= -.63	.533
Gender (Males/Females)	15/22	5/11	x^2= .41	.522
Years of education	16.05 (3.64)	14.72 (3.97)	t (56)= 1.19	.238
Alcohol (units/week)	8.28 (9.43)	7.19 (10.23)	t (56)= .38	.706
BMI**	25.28 (3.75)	30 (5.59)	t (56)= -3.59	.001*

*Significant difference between Changers and No-changers (p< .001).

**BMI= Body Mass Index

5.5.2 Differences between Changers and No-changers in the three groups

In order to test the hypothesis, I examined any possible changes at the amount of brisk walk over time for the "Changers" versus the "No-changers", in each of the participants groups (Mindfulness, Lifestyle, Control).

In the Mindfulness group (N= 16) there were 6 Changers and 10 No-changers. Since the data in this sample were not normally distributed, I performed the non-parametric test Kruskal-Wallis H. As expected, this test showed no statistical differences between Changers and No-changers at baseline $\chi^2(1) = 1.47$, $p = .226$, right after the intervention $\chi^2(1) = 0.50$, $p = .480$, or at the 6 months follow-up $\chi^2(1) = 0.48$, $p = .826$. Moreover, because the sample was too small for a statistical analysis, I have also reported the median, mean and standard deviation for the three timepoints (Table 5.2).

Table 5.2 Amount of brisk walking (minutes/week) for Changers and No-changers in the Mindfulness group

	Changers N=6		**No-changers N= 10**		
	Median	**Mean (Std. Dev)**	**Median**	**Mean (Std. Dev)**	**p-value**
Baseline	5	88.33 (151.61)	110	138 (138.31)	.226
Post-Intervention	112.50	154.17 (112.50)	180	233.10 (228.94)	.480
6 Months	45	75.83 (90.08)	35	112.30 (150.48)	.826

The Lifestyle group was the one where I would expect that Changers would me more likely to change (increase brisk walk minutes) compared to No-changers. In this group (N= 16) there were 8 Changers and 8 No-changers. Changers versus No-changers did not differ at baseline $\chi^2(1) = 2.84$, $p = .092$ but, there was a marginally significant difference between the two groups right after the end of the intervention $\chi^2(1) = 3.38$, $p = .066$. However, these results contradict the hypothesis as No-changers were the ones who reported more minutes of brisk walk than Changers.

There were no differences for the 6 months follow-up and all results are presented in Table 5.3.

Table 5.3 Amount of brisk walking (minutes/week) for Changers and No-changers in the Lifestyle group

	Changers N= 8		**No-changers N= 8**		
	Median	**Mean (Std. Dev)**	**Median**	**Mean (Std. Dev)**	**p-value**
Baseline	37.50	93.13 (151.33)	185	216.25 (148.20)	.092
Post-Intervention	70.50	95.89 (86.50)	280	247.38 (163.20)	.066
6 Months	97.50	102.50 (91.46)	265	221.25 (200.76)	.368

Lastly, the Control group (N= 21) was consisted of 10 Changers and 11 No-changers. The only difference between the two groups was at baseline $\chi^2(1) = 6.62$, $p = .010$. As shown in Table 5.4, the comparisons right after the intervention $\chi^2(1) = .361$, $p = .548$ and at the 6 months follow-up $\chi^2(1) = .50$, $p = .481$ were not significant.

Table 5.4 Amount of brisk walking (minutes/week) for Changers and No-changers in the Control group.

	Changers N= 10		**No-changers N= 11**		
	Median	**Mean (Std. Dev)**	**Median**	**Mean (Std. Dev)**	**p-value**
Baseline	70	70.51 (53.55)	160	188.55 (120.38)	.010*
Post-Intervention	51.50	289.62 (659.62)	135	154.09 (121.34)	.548
6 Months	62.50	160.30 (228.01)	125	135.09 (102.35)	.481

5.6 Discussion

The scope of this chapter was to examine whether Readiness to change can predict change in the behaviour of people with Subjective Cognitive Decline. In order to assess this, I examined people who stated that were willing to change against people who did not intend to change, in all three groups: Mindfulness, Lifestyle and Control.

Having assessed their Readiness to Change at baseline, I also asked them to report the amount of brisk walk they would do in a typical week. Following that, they would start their interventions (or 4 weeks of waiting for the Control group) and then report again how many minutes of brisk walk they did the week after the end of the intervention and 6 months later. Given that people in the Lifestyle group were assigned the task of minimum 15-minute brisk walks three times a week, I hypothesised that participants in this group who also stated that are willing to change, would significantly increase their amount of exercise, compared to people who stated no intention for a change. I also compared Changers and No-changers regarding their demographic details.

5.6.1 Demographic data

Looking at the two groups of Changers and No-changers at baseline, one can notice that their only significant difference is their BMI. No-changers seem to have a higher BMI than Changers. Unfortunately, this is just an observation and it is hard to draw any conclusions, due to the small size of the sample.

5.6.2 Differences between Changers and No-changers in the three group

Regarding the comparison between the three participant groups, the results were contradictory to the hypothesis. It is worth mentioning again that due to the small size of the sample, I can only speculate without drawing conclusions.

In the Mindfulness group, the pattern was the same regardless of whether participants were intending to change or not: their amount of exercise went up post-intervention and 6 months later, it returned to the baseline level. In the Lifestyle group, all participants increased their brisk walk after the intervention. Moreover, this trend was maintained by Changers until the 6 months follow-up but not for the No-changers. Even though these changes were not significant in this small sample, it is worth noticing the trend and trying to verify it in the future with a bigger sample. Regarding the Control group, both groups exercised less over time and the only difference was the fact that No-changers exercised more than Changers at baseline.

Despite the absence of statistically significant differences between Changers and No-Changers in the Lifestyle group, I believe it is interesting to observe the big variations in the amounts of exercise reported. In some case, there were participants who reported nearly zero minutes of brisk walking while, other would report more than 3 hours in a week. This could be indicative of the diversity of a group like people with Subjective Cognitive Decline but also, of the disadvantages of self-reported measurements. An objective measurement of physical exercise, along with a bigger sample would help to better estimate the exact activity of participants and possibly establish a relationship between Readiness to change and behavioural changes.

Chapter 6 ApoE genotype and Subjective Cognitive Decline: A pilot study

Memory complaints in the absence of any diagnosis might be a pre-clinical manifestation of dementia. The E4 copy of Apolipoprotein E (ApoE) is the major genetic risk factor for Alzheimer's Disease (AD). This chapter discusses the relationship between the ApoE status and cognitive function in people with memory complaints who do not have dementia. This group of cognitively healthy people falls within the category of Subjective Cognitive Decline (SCD). As genetic studies require a larger sample, this pilot study has an exploratory scope and constitutes part of a bigger project (DECODE study).

6.1 Introduction

6.1.1 ApoE and Cognition

The ApoE gene has been linked to faster memory decline and poorer memory performance in patients with Alzheimer's Disease (AD) (Cosentino et al., 2008). There are 3 common versions (alleles) of the gene: E2, E3 and E4 and everyone inherits two, one from each parent. Therefore, people will have one of the following six combinations of alleles, what is known as "genotype": E2/2, E2/3, E2/4, E3/3, E3/4 and E4/4. Table 6.1 depicts the proportion of each genotype that has been observed in US population and AD risk.

Table 6.1 Frequency of different ApoE genotypes in US citizens and AD risk (Raber, Huang, & Ashford, 2004)

Genotype	Population[a] (%)	AD[b] (%)	Population (M= Millions)	AD (M= Millions)
E2/2	1	0.1	0.5M	0.004M
E2/3	12	4	5.5M	0.18M
E3/3	60	35	27.6M	1.4M
E3/4	21	42	9.6M	1.7M
E4/4	2	16	0.9M	0.6M

Note. E2/4 carriers were not included in this publication.

[a] With an estimate of 46 million US citizens who were aged over 60 years old in 2000.

[b] With the assumption that 4 million people have been diagnosed with AD.

(Raber et al., 2004)

The E4 allele is the single major genetic risk factor for sporadic AD. Around 80% of familial and 64% sporadic late onset AD patients have at least one copy of the E4 allele, in comparison to 31% of controls (Corder et al., 1993). There is also evidence that E4 can lead to earlier onset of AD and affect the rate of cognitive decline in preclinical AD (Heffernan, Chidgey, Peng, Masters, & Roberts, 2016). People who carry at least one copy of the E4 allele have 3-4 times increased risk of developing the disease, while in homozygotes (people with two copies of the E4) the risk is 8-12 time higher when compared to E2, the allele that has been suggested to have a protective effect against AD (Corder et al., 1994; Verghese, Castellano, & Holtzman, 2011). However, carrying the E4 allele is not a determinant of the disease and not all E4 homozygotes develop AD. An interesting study has shown that 50% of E4 homozygotes made it to the age of 80 years without developing AD (Farrer et al., 1995). The prevalence of the alleles E2, E4 around the globe is around 7 and 14% respectively, while for the E3 which has been suggested as a neutral isoform it is 79% (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). Figure 6.1 depicts the prevalence of the E4 allele in AD population, stratified by region.

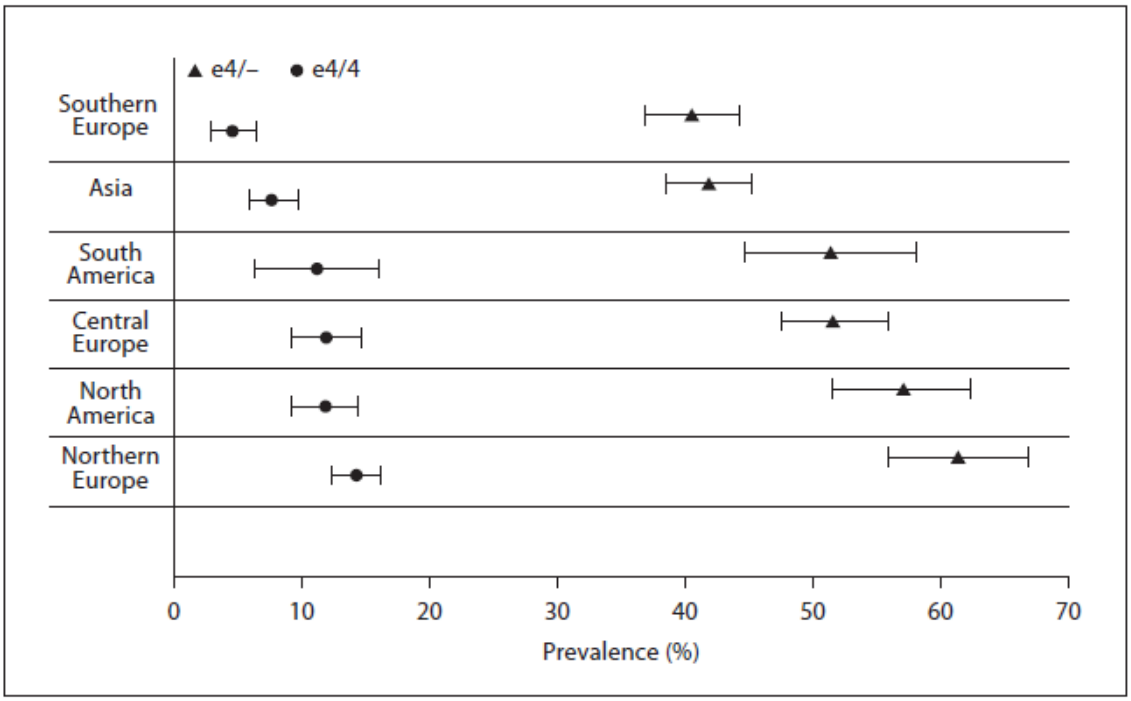

Figure 6.1 Prevalence of the Apoe E4 allele (one and two copies) in the AD population, by region (Ward et al., 2012)

6.1.2 ApoE and Subjective Cognitive Decline

As discussed in the Introduction chapter, Subjective Cognitive Decline (SCD) refers to a subjective worsening of cognitive functions compared to a previous state and might serve as a pre-symptomatic indicator of AD. Many researchers have stated that AD requires interventions before the manifestation of clinical symptoms and SCD constitutes an interesting group to be investigated, as individuals with this condition are at a higher risk of developing the disease (Risacher et al., 2015). Despite the well-known risk factor that ApoE E4 allele plays in AD, few studies have investigated the role of it in the SCD population. The first study to examine this was conducted by Small and his colleagues (1999) who showed an over-representation of the E4 allele in individuals with SCD but, its effect on this group's cognitive function is yet to be explored. A later study has reported that even at the early stages when cognitive deficits cannot be detected through tests, memory complaints and E4 allele carriage are both risk factors for cognitive decline. Moreover, a combination of these events can have an additive effect on cognitive impairment (Dik et al., 2001). This evidence is supported by a most recent study, where researchers have observed abnormal changes in tau and amyloid biomarkers in individuals with SCD who are E4 carriers (Risacher et al., 2015).

6.2 Objective

The purpose of this chapter is twofold. Firstly, this chapter aims to further explore the assumption that people with memory complaints who are also E4 carriers, are at higher risk of cognitive decline. I hypothesised that in this sample of people with SCD, participants who carry the E4 allele will show poorer performance on the cognitive tests compared to non-carriers and the reverse pattern will be seen with E2 carriers. The second aim of the chapter is to explore the demographic characteristics and psychological function of the E4 carriers and the E2 carriers versus non-carriers, in our SCD sample. As described earlier these alleles have been suggested to put at higher risk or protect the carriers respectively, hence the focus of this chapter will be solely on them.

6.3 Tasks and procedure

According to the DECODE protocol, the blood samples were collected at the Brain Centre in North Bristol NHS Trust, by myself, after completing the Venepuncture training course and assessment at North Bristol NHS Trust. Upon their collection, I centrifuged them on site and stored them at -80 °C freezers. Later, they were collected by one of the team's colleagues from the University of West of England (UWE) and transferred there in order to be genotyped. Genotyping of ApoE was assessed according to methods described in (Miners et al., 2009).

Given the scope of this study, genetic counselling was beyond the remit and hence the genotyping results were not relayed to the participants (as per British Society for Human Genetics guidelines (http://www.bshg.or.uk). This decision was based on the fact that the Concordat and Moratorium on Genetics and Insurance (DoH in discussion with ABI-updated 2014) states that predictive genetic testing does not need to be disclosed to insurers as they are part of a research project. Furthermore, I did not want to add any extra burden to the participants given the uncertainty that would remain in the absence of a proper clinical examination. The non-disclosure of the genetic testing results was clearly stated in the Participant Information sheet. After receiving the genotyping report from the colleagues at UWE, we performed the statistical analysis.

As mentioned at the beginning of this chapter, this pilot study constitutes part of the DECODE project and all participants undertook the tests we have described in the Methods section. Even though the DECODE protocol included three visits in total, in this chapter I am only focusing on the baseline assessment as we do not aim to explore any post-intervention performance.

The baseline assessment included collection of demographic characteristics (Background questionnaire and Cognitive Reserve Index questionnaire-CRIq), a Cognitive Test battery and questionnaires to measure Psychological functions. In more detail, the demographic characteristics collected included questions about their age, yeas of education, area of residence, smoking, exercise, mindfulness, BMI (Body Mass Index), depression history, anxiety history, medical conditions (blood pressure, cholesterol, diabetes, stroke, heart disease, neurological conditions, psychiatric conditions) and handedness. In this chapter I am reporting the most relevant variables of interest and more information can be found in the Appendix.

Cognitive function was measured in the areas of verbal memory (RAVLT), verbal functioning (Letter fluency and Semantic fluency) and working memory (N2 reaction time and accuracy). I also tested for performance validity (TOMM), visual attention and task switching (Trail Making Test A and B) and administered the MoCA to detect cognitive impairment and briefly assess memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language and orientation.

Regarding the Psychological variables of interest, I measured health anxiety (HAI), depression, anxiety and stress (DASS) and well-being (WHO). Finally, I measured mindfulness (FFMQ) and self-reported levels of functional memory disorder (FMDQ). For more information on the tests and questionnaires please refer to General Methods.

6.4 Participants

For the DECODE study, 100 participants were tested: 90 with SCD and 10 with Functional Cognitive Disorder (FCD) at the baseline visit and asked them to consent to an optional blood sample. I collected

75 blood samples but 13 of them could not be genotyped. This could be either because the samples had a low amount of DNA leading to the PCR (Polymerase Chain Reaction) not working correctly, or the DNA amount was sufficient but the digestion of the DNA with the appropriate restriction enzymes did not work and the separate bands could not be seen. 7 remaining participants did not give consent to the blood test, 9 dropped out and we failed to obtain blood from 9 participants due to thin veins.

I ended up with 62 samples (SCD=57 and FCD=5) but, for the purposes of this pilot study I further excluded the FCD participants as the sample was too small and not equivalent to the SCD sample. In addition to that, I excluded 2 SCD participants who were both E2 and E4 carriers (E2/4 genotype). Finally, 55 SCD participants with a known genotype were included in the analysis. Throughout this analysis, the term "carrier" refers to individuals who have at least one copy of the allele, meaning being both homozygotes (2 copies) and heterozygotes (1 copy). The numbers of carriers versus non-carriers are depicted in Table 6.2.

Table 6.2 E4 and E2 carriers versus non-carriers

		N
ApoE- E4	Carrier	13
	Non-carrier	42
ApoE- E2	Carrier	7
	Non-carrier	48

6.5 Results

Statistical analysis performed was independent sample t-tests where data were normally distributed and the Mann-Whitney U test for the tests where the data were not normally distributed. There is no correction for multiple comparisons (Bonferroni correction) as this is an exploratory analysis.

6.5.1 Cognitive performance of SCD E4 and E2 carriers versus non-carriers

I hypothesised that, people with SCD who are also E4 carriers will have poorer performance on cognitive testing, compared to people with SCD who do not carry the E4 allele.

I detected differences between E4 carriers and non-carriers on the TOMM test (Table 6.3). All other comparisons were non-significant (Table 6.3 and Table 6.4).

Table 6.3 Comparing Cognitive scores for E4 carriers versus non-carriers

	Mean (Std. Dev) /Median	Mean (Std. Dev) /Median	t-test/ Mann-Whitney U test	Sig. (p)
	E4 carriers (N=13)	**Non-carriers (N= 42)**		
RAVLT LD	8.38 (2.90)	8.60 (3.39)	t (53) = .20	.841
Letter fluency	38.62 (9.26)	42.43 (9.26)	t (53)= 1.30	.200
Semantic fluency	20.77 (3.98)	22.19 (5.39)	t (53)= .88	.384
N2 reaction time	828.63 (155.03)	733.48 (166.75)	t (53) = -1.83	.073
N2 accuracy	84.36 (9.68)	86.19 (6.06)	t (53)= .82	.417
N3 reaction time	901.13 (173.25)	789.95 (182.45)	t (53)= -1.99	.051
N3 accuracy	73.08 (7.23)	77.14 (6.45)	t (53)= 1.93	.059
Trail A	27.46 (7.25)	28.64 (9.08)	t (53)= .43	.670
Trail B	74.85 (32.95)	70.51 (28.75)	t (53)= -.46	.649
TOMM**	50	49	U= 157	.012***
MoCA**	28	28	U= 211.50	.217

*RAVLT LD= Rey Auditory Verbal Learning Test, Long delay, N2 = N-back test for N=2, N3 = N-back test for N=3, Trail A and B= Trail Making Test A and B, TOMM= Test of Memory Malingering, MoCA= Montreal Cognitive Assessment.

**The non-parametric Mann-Whitney U test was used as scores for these tests were not normally distributed.

*** Significant difference between E4 carriers and non-carriers ($p<0.05$).

Table 6.4 Comparing Cognitive scores for E2 carriers versus non-carriers

	Mean (Std. Dev) /Median	Mean (Std. Dev) /Median	t-test/ Mann-Whitney U test	Sig. (p)
	E2 carriers (N= 7)	**Non-carriers (N= 48)**		
RAVLT LD	9 (2.58)	8.48 (3.36)	t (53)= -.39	.697
Letter fluency	43.86 (8.91)	41.19 (9.42)	t (53)= -.71	.484
Semantic fluency	21.14 (3.89)	21.96 (5.27)	t (53)= .39	.696
N2 reaction time	676.36 (83.72)	767.58 (174.15)	t (53)= -.13	.181
N2 accuracy	86.90 (6.19)	85.59 (7.18)	t (53)= -.71	.648
N3 reaction time	822.14 (164.48)	812.74 (189.71)	t (53)= -.12	.902
N3 accuracy	78.10 (5.73)	75.90 (6.95)	t (53)= -.79	.431
Trail A	23.71 (7.78)	29.04 (8.61)	t (53)= 1.66	.128
Trail B	73.14 (30.55)	71.32 (29.73)	t (52)= -.15	.881
TOMM**	49	50	U= 152	.702
MoCA**	27	28	U= 165	.951

*RAVLT LD= Rey Auditory Verbal Learning Test, Long delay, N2 = N-back test for N=2, N3 = N-back test for N=3, Trail A and B= Trail Making Test A and B, TOMM= Test of Memory Malingering, MoCA= Montreal Cognitive Assessment.

**The non-parametric Mann-Whitney U test was used as scores for these tests were not normally distributed.

6.5.2 Psychological differences between E4 and E2 carriers and non-carriers

The second objective was to explore differences in psychological factors between E4 carriers and non-carriers and E2 carriers and non-carriers in people with SCD. Tables 6.5 and 6.6 show that on the "Describe" facet of the mindfulness questionnaire E4 carriers reported lower scores and E2 carriers reported higher scores compared to non-carriers. Furthermore, E4 carriers reported higher scores on the Depression and Stress scales compared to non-carriers and lower scores on the well-being questionnaire (Table 6.5).

All other comparisons were non-significant (Table 6.5 and Table 6.6).

Table 6.5 Comparing scores on Psychological questionnaires for E4 carriers versus non-carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test	Sig. (p)	Cohen's *d*
	E4 carriers (N= 13)	**Non-carriers (N= 42)**			
HAI Total	14.77 (6.65)	12.40 (5.37)	t (53)= -1.31	.195	
FFM Observe	23.08 (5.04)	25.60 (5.78)	t (53)= 1.41	.164	
FFM Describe	22.54 (5.16)	27.79 (5.92)	t (53)= 2.87	.006***	.945
FFM Awareness	21.92 (7.37)	24.79 (5.46)	t (53)= 1.52	.135	
FFM Non judge	26 (6.03)	29.17 (5.96)	t (53)= 1.67	.101	
FFM Non react	18.54 (6.09)	21.17 (5.01)	t (53)= 1.57	.122	
FMDQ Total	7.38 (2.10)	6.19 (2.14)	t (53)= -1.76	.084	
DASS Depression	12.62 (11.56)	6 (8.11)	t (53)= -2.31	.025**	.663
DASS Anxiety	7.69 (7.61)	4.40 (5.53)	t (53)= -1.71	.093	
DASS Stress	16.31 (10.03)	9.98 (7.55)	t (53)= -2.44	.018**	.713
DASS Total	36.62 (25.11)	20.38 (17.62)	t (53)= -2.62	.012**	.748
WHO	11.62 (5.08)	15.83 (4.35)	t (53)= 2.94	.005***	.890

*HAI= Health Anxiety Inventory, FFM= Five Facet Mindfulness questionnaire (Five facets: Observing, Describing, Acting with awareness, non-judging of inner experience and non-reactivity to inner experience), FMDQ= Functional Memory Disorder questionnaire, DASS= Depression, Anxiety and Stress scale, WHO= World health Organisation well-being questionnaire.

**Significant difference between E4 carriers and non-carriers ($p<0.05$).

***Significant difference between E4 carriers and non-carriers ($p<0.01$).

Table 6.6 Comparing scores on Psychological questionnaires for E2 carriers versus non-carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test	Sig. (p)	Cohen's *d*
	E2 carriers (N= 7)	**Non-carriers (N= 48)**			
HAI Total	12.71 (4.92)	13.00 (5.87)	t (53)= .12	.903	
FFM Observe	26.71 (6.40)	24.75 (5.59)	t (53)= -.85	.397	
FFM Describe	31.71 (6.99)	25.79 (5.69)	t (53)= -2.50	.015**	.928
FFM Awareness	27.57 (5.62)	23.60 (5.96)	t (53)= -1.66	.104	
FFM Non judge	29.57 (6.60)	28.25 (6.05)	t (53)= -.53	.595	
FFM Non react	20.71 (4.23)	20.52 (5.52)	t (53)= -.09	.930	
FMDQ Total	6.14 (1.68)	6.52 (2.25)	t (53)= .43	.672	
DASS Depression	6.29 (9.83)	7.75 (9.39)	t (53)= .38	.703	
DASS Anxiety	6 (10.71)	5.06 (5.39)	t (53)= -.37	.711	
DASS Stress	12.86 (11.77)	11.27 (8.12)	t (53)= -.46	.651	
DASS Total	25.14 (29.53)	24.08 (19.39)	t (53)= -.13	.900	
WHO	15.57 (5.23)	14.73 (4.82)	t (53)= -.43	.671	

*HAI= Health Anxiety Inventory, FFM= Five Facet Mindfulness questionnaire (Five facets: Observing, Describing, Acting with awareness, non-judging of inner experience and non-reactivity to inner experience), FMDQ= Functional Memory Disorder questionnaire, DASS= Depression, Anxiety and Stress scale, WHO= World health Organisation well-being questionnaire.

**Significant difference between E2 carriers and non-carriers ($p<0.05$).

6.5.3 Demographic differences between E4 and E2 carriers and non-carriers

I further compared the E4 and E2 carriers versus non-carriers based on various demographic variables. Table 6.7 shows that there were differences between E4 carriers and non-carriers on BMI interpretation and that E4 carriers were more likely to have history of Anxiety, compared to non-carriers. Table 6.8 depicts the differences on BMI interpretation and gender for E2 carriers versus non-carriers. I also observed that E2 carriers were less likely to have a history of Anxiety when compared to non-carriers. All other comparisons were non-significant.

Table 6.7 Demographic differences between E4 carriers and non-carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test/ x^2	Sig. (p)
	E4 carriers (N= 13)	**Non-carriers (N= 42)**		
Age (years)*	63.38 (9.73)	64.76 (9.15)	t (53)= .47	.642
Education (years)*	15.62 (3.97)	15.87 (3.92)	t (53)= .20	.840
Exercise	10 Yes	33 Yes	x^2= .02	.900
	3 No	9 No		
CRIq	129.92 (19.30)	136.71 (15.34)	t (53)= 1.31	.196
Gender	3 Males 10 Females	17 Males 25 Females	$x^{2=}$ 1.30	.254
BMI	24.18 (4.22)	27.88 (4.79)	t (52)= 2.49	0.16
BMI^	9 Healthy	12 Healthy	x^2= 6.72	.035**
	3 Overweight	19 Overweight		
	1 Obese	10 Obese		
Anxiety history	7 Yes	7 Yes	x^2= 7.23	.007***
	6 No	35 No		
Depression history	5 Yes	16 Yes	x^2= 3.34	.188
	7 No	26 No		
Family history of AD	8 Yes	23 Yes	x^2= .44	.804
	5 No	18 No		

^BMI= Body Mass Index.

*As these are numeric variables measured in years, we used t-tests to compare them. For the rest of the variables we used Chi-square tests.

**Significant difference between E4 carriers and non-carriers ($p<0.05$).

***Significant difference between E4 carriers and non-carriers ($p<0.01$).

Table 6.8 Demographic differences between E2 carriers and non-carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test/ x^2	Sig. (p)
	E2 carriers (N= 7)	**Non-carriers (N= 48)**		
Age (years)*	66.71 (5.82)	64.10 (9.61)	t (53)= -.70	.489
Education (years)*	14.07 (3.54)	16.06 (3.92)	t (53)= 1.27	.210
Exercise	4 Yes	39 Yes	x^2= 2.08	.149
	3 No	9 No		
CRIq*	130.43 (14.25)	135.79 (16.75)	t (53)= .80	.425
Gender	0 Males	20 Males	x^2= 4.58	.032**
	7 Females	28 Females		
BMI*	28.85 (6.41)	26.71 (4.64)	t (52)= -1.08	.285
BMI^	3 Healthy	18 Healthy	x^2= 8.65	.013**
	0 Overweight	22 Overweight		
	4 Obese	7 Obese		
Anxiety history	0 Yes	14 Yes	x^2= 2.74	.098
	7 No	34 No		
Depression history	2 Yes	19 Yes	x^2= .51	.773
	5 No	28 No		
Family history of AD	5 Yes	26 Yes	x^2= .81	.669
	2 No	21 No		

^BMI= Body Mass Index.

*As these are numeric variables measured in years, we used t-tests to compare them. For the rest of the variables we used Chi-square tests.

**Significant difference between E2 carriers and non-carriers ($p<0.05$).

6.5.4 Differences between E2 and E4 carriers

E2 and E4 carriers were also compared regarding their performance on cognitive tests and psychological questionnaires as well as their demographic characteristics. I found that E2 carriers were significantly faster than E4 carriers on the N2-back test (Table 6.9) while, all other comparisons were non-significant.

Table 6.9 Comparing Cognitive scores for E2 versus E4 carriers

	Mean (Std. Dev) /Median	Mean (Std. Dev) /Median	t-test/ Mann-Whitney U test	Sig. (p)	Cohen's *d*
	E2 carriers (N= 7)	**E4 carriers (N= 13)**			
RAVLT LD	7.86 (2.55)	8.15 (2.41)	t (18)= .47	.645	
Letter fluency	43.86 (8.92)	38.62 (9.26)	t (18)= 1.22	.237	
Semantic fluency	21.14 (3.89)	20.77 (3.98)	t (18)= .20	.842	
N2 reaction time	676.36 (83.72)	828.63 (155.03)	t (18)= -2.40	.028**	1.222
N2 accuracy	86.90 (6.19)	84.36 (9.68)	t (18)= .63	.539	
N3 reaction time	822.14 (164.48)	901.13 (173.25)	t (18)= -.99	.336	
N3 accuracy	78.10 (5.73)	73.08 (7.23)	t (18)= 1.58	.131	
Trail A	23.71 (7.78)	27.46 (7.25)	t (18)= -1.08	.296	
Trail B	73.14 (30.55)	74.85 (32.95)	t (18)= -.11	.911	
TOMM**	49	50	U= 26	.135	
MoCA**	27	28	U= 37	.536	

*RAVLT LD= Rey Auditory Verbal Learning Test, Long delay, N2 = N-back test for N=2, N3 = N-back test for N=3, Trail A and B= Trail Making Test A and B, TOMM= Test of Memory Malingering, MoCA= Montreal Cognitive Assessment.

**The non-parametric Mann-Whitney U test was used as scores for these tests were not normally distributed.

*** Significant difference between E2 and E4 carriers ($p<0.05$).

After comparing their performance on psychological questionnaires, I observed that E2 carriers scored higher than E4 carriers on the "Describe" scale of the Five Facet Mindfulness questionnaire (Table 6.10). No other significant differences were reported for the rest of the questionnaires.

Table 6.10 Comparing scores on Psychological questionnaires for E2 and E4 carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test	Sig. (p)	Cohen's *d*
	E2 carriers (N= 7)	**E4 carriers (N= 13)**			
HAI Total	12.71 (4.92)	14.77 (6.65)	t (18)= -.72	.484	
FFM Observe	26.71 (6.40)	23.08 (5.04)	t (18)= 1.40	.178	
FFM Describe	31.71 (6.99)	22.54 (5.16)	t (18)= 3.36	.004**	1.492
FFM Awareness	27.57 (5.62)	21.92 (7.37)	t (18)= 1.76	.095	
FFM Non judge	29.57 (6.60)	26 (6.03)	t (18)= 1.22	.237	
FFM Non react	20.71 (4.23)	18.54 (6.09)	t (18)= .84	.413	
FMDQ Total	6.14 (1.68)	7.38 (2.10)	t (18)= -1.34	.196	
DASS Depression	6.29 (9.83)	12.62 (11.56)	t (18)= -1.23	.236	
DASS Anxiety	6 (10.71)	7.69 (7.61)	t (18)= -.41	.685	
DASS Stress	12.86 (11.77)	16.31 (10.03)	t (18)= -.69	.498	
DASS Total	25.14 (29.53)	36.62 (25.11)	t (18)= -.92	.371	
WHO	15.57 (5.26)	11.62 (5.08)	t (18)= 1.64	.118	

*HAI= Health Anxiety Inventory, FFM= Five Facet Mindfulness questionnaire (Five facets: Observing, Describing, Acting with awareness, non-judging of inner experience and non-reactivity to inner experience), FMDQ= Functional Memory Disorder questionnaire, DASS= Depression, Anxiety and Stress scale, WHO= World health Organisation well-being questionnaire.

**Significant difference between E2 and E4 carriers ($p<0.01$).

Finally, I found that E2 carriers were more likely to be females, with higher Body Mass Index (BMI) and fewer of them had anxiety history compared to E4 carriers (Table 6.11).

Table 6.11 Demographic differences between E2 and E4 carriers

	Mean (Std. Dev)	Mean (Std. Dev)	t-test/ x^2	Sig. (p)
	E2 carriers (N= 7)	**E4 carriers (N= 13)**		
Age (years)*	66.71 (5.82)	63.38 (9.73)	t (18)= .82	.421
Education (years)*	14.07 (3.54)	15.62 (3.97)	t (18)= -.86	.401
Exercise	4 Yes	10 Yes	x^2= 2.14	.343
	3 No	3 No		
CRIq*	130.43 (14.25)	129.92 (19.30)	t (18)= .06	.952
Gender	0 Males	3 Males	x^2= 6.74	.034**
	7 Females	10 Females		
BMI*	28.85 (6.41)	24.18 (4.22)	t (18)= 1.97	.065
BMI^	3 Healthy	9 Healthy	x^2= 16.72	.002***
	0 Overweight	3 Overweight		
	4 Obese	1 Obese		
Anxiety history	0 Yes	7 Yes	x^2= 8.23	.016**
	7 No	6 No		
Depression history	2 Yes	5 Yes	x^2= 3.55	.471
	5 No	7 No		
Family history of AD	5 Yes	8 Yes	x^2= 1.71	.788
	2 No	5 No		

^BMI= Body Mass Index.

*As these are numeric variables measured in years, we used t-tests to compare them. For the rest of the variables we used Chi-square tests.

**Significant difference between E2 and E4 carriers ($p<0.05$).

***Significant difference between E4 carriers and non-carriers ($p<0.01$).

6.6 Discussion

The ApoE E4 allele is the major genetic risk factor for AD and has been linked to faster cognitive decline and poorer memory not only in people with AD (Cosentino et al., 2008), but also in people with Mild Cognitive Impairment (MCI) (Farlow et al., 2004; Wang, Lirng, Lin, Chang, & Liu, 2006). Another risk factor for future AD is SCD which has been suggested to potentially be a pre-clinical manifestation of the disease. However, there is limited evidence about the role of the E4 copy in the SCD population. In one project researchers observed that E4 carriers with SCD scored significantly worse on episodic memory, compared to non-carriers (Striepens et al., 2011). In addition to that, two studies have shown an over-representation of E4 in an SCD group compared to healthy individuals (Laws et al., 2002; G. W. Small et al., 1999) whereas another study did not validate such findings (Harwood, Barker, Ownby, Mullan, & Duara, 2004).

Given the limited literature on the relationship between SCD and the E4 allele, I decided to follow the a priori hypothesis (stated in Objectives), that individuals with SCD who are also E4 carriers will have poorer performance on cognitive testing compared to the SCD non-carriers.

6.6.1 Cognitive performance of SCD E4 and E2 carriers and non-carriers

I compared SCD E4 and E2 carriers with non-carriers on several cognitive tests and observed that E4 carriers were more likely to score higher on the TOMM test compared to E4 non-carriers. An outlier was spotted, who scored quite low on TOMM but was still above the cut-off point. Even after removing the outlier though, the difference between E4 carriers and non-carriers would remain. This is an unusual and unexpected finding especially since the difference between the medians is very small (1 point). This is more likely to be a finding by chance and would not actually suggest a better performance of the carriers in clinical practice.

Moreover, despite the absence of significant difference on the N-back test (N2 and N3), there could possibly be a trend of E4 carriers being slower on the measurement of working memory (N2 reaction time and N3 reaction time and accuracy). Moreover, E2 carriers were faster when compared with E4 carriers. Interestingly, a recent study has suggested that working memory might precede and predict episodic memory impairment (Memel, Woolverton, Bourassa, & Glisky, 2018). It would therefore be a valuable metric to predict changes in the cognitive domain not only for ageing studies but also for the clinical setting. Such findings also support the hypothesis that carriers of the E4 allele might be at extra risk of future cognitive impairment, even at a time when no clinical symptoms have been observed yet. However, these results should be interpreted with caution as our sample was very small, and no other significant differences were suggested regarding the rest of the cognitive testing.

6.6.2 Psychological differences between E4 and E2 carriers and non-carriers

When looking for any differences between carriers and non-carriers with regards to psychological variables, the most important finding was that E4 carriers score lower on FFM Describe scale compared to non-carriers and E2 carriers. On the contrary, E2 carriers score significantly higher than non-carriers. The Describe facet of the FFM questionnaire refers to labelling the internal experiences with words (Baer et al., 2008) and it has been shown that it correlates negatively with Depression (Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011). This is an interesting finding showing that more mindful people might be less prone to depression and low mood. Additionally, when I looked for any differences between the E2 and E4 carriers, I found that E2 carriers scored higher on the "Acting with awareness" facet but the result was not significantly different. This subscale describes the way individuals are aware of their actions and pay attention to the present moment instead of behaving mechanically (Baer et al., 2008). This facet also correlates negatively with depression (Bohlmeijer et al., 2011) suggesting that having the E2 allele might make people more aware of their actions and less prone to depression but this is not an assumption that can be generalised due to the lack of statistical power and the size of the sample.

These findings are complimented by a significant difference on the Depression, Anxiety and Stress scale (DASS) as well as the World Health Organisation well-being questionnaire (WHO). E4 carriers reported higher levels of depression and stress compared to non-carriers and lower levels of well-being. This supports the hypothesis that SCD symptoms might be a depressive manifestation (Balash et al., 2013) and suggests a relationship between the E4 allele and depression/stress. These findings replicate previous studies that have found higher frequency of the E4 allele in elderly patients with depression (Krishnan et al., 1996) and have suggested E4 as a predictor of future clinical depression (Skoog et al., 2015). In that last study, the power of E4 allele as a depression predictor was still significant even after excluding the participants who later developed dementia, suggesting a dementia-independent link between the E4 allele and depression (Skoog et al., 2015).

Considering the comorbidity of anxiety and subjective memory complaints (Balash et al., 2013), we need longitudinal studies that will examine whether there is a link between E4 allele, depression and later development of AD, or if E4 carriers with SCD are at a higher risk of developing depression, regardless of their risk for developing dementia.

6.6.3 Demographic differences between E4 and E2 carriers and non-carriers

Lastly, I compared the group in reference to the demographic variables collected and explored if any of these would differentiate E4 and E2 carriers versus non-carriers and E4 versus E2 carriers in our SCD

sample. Having a history of anxiety was frequent in E2 carriers compared to non-carriers but such difference was not significant. Interestingly, I found that E4 carriers were more likely to have history of anxiety compared to non-carriers and E2 carriers. These results suggest that having memory complaints and being an E4 carrier might have an additive effect to the experience of anxiety in the lifespan but, cannot be generalised due to the lack of statistical power and the size of the sample.

What came as a surprise was that there were no differences for family history of AD between the groups. This could be due to selection/recruitment bias as more than half of the participants had family history of AD and this could potentially explain their drive to participate in research or even part

Furthermore, a difference regarding gender and Body Mass Index (BMI) was reported. It was found that E2 carriers were more likely to be females and have a higher BMI than non-carriers and E4 carriers. There is not any literature available regarding the gender difference and we speculate that this could be due to recruitment bias, since there were more female participants (N= 35) than males (N= 20). Regarding the relationship between E2 and BMI, our findings are in accordance with genetic studies that have proposed a link between E2 allele and higher BMI (Duman, Ozturk, Yilmazer, & Hatemi, 2004; Zeljko et al., 2011). It has also been suggested that E2 might be a genetic modifier for higher risk of developing Type 2 diabetes and obesity (Kuhel et al., 2013). However, this relationship has not been established and such inference would be better supported by a larger number of participants.

To my knowledge, no one has looked at the differences on cognitive tests, psychological factors and demographic characteristics in SCD people based on their ApoE genotype so far. This pilot study had an exploratory nature and aimed firstly, to identify potential predictors of cognitive performance in the SCD population and secondly, to describe the psychological factors and characteristics of people with SCD based on whether they hold the high risk/protective alleles or not. These findings suggest that being an E2 carrier could predict better performance on working memory and visual attention tasks while, carrying the E4 allele could affect an individual's risk of depression, anxiety and stress. An interesting finding that needs further investigation is the relationship between E2 carriage and BMI, as this could be a helpful predictor of future risk of cognitive impairment in the SCD population.

Chapter 7 Relationship between Health Anxiety, Cognitive Performance and Well-being

This chapter will examine whether Health Anxiety might affect the performance of people with SCD and FCD, on cognitive and psychological outcome measures.

7.1 Introduction

7.1.1 Subjective Cognitive Decline

Alzheimer's Disease (AD) which is the most common type of dementia, is a neurodegenerative disease leading to problems with memory and cognitive function (C. R. Jack, 2012). Its incidence increases with age (Archer, 2015) but by the moment a clinical diagnosis can be made, significant brain cell loss has already occurred (Ridha et al., 2006). The fact that irreversible changes in brain structure might have occurred up to 20 years before the diagnosis (Figure 7.1), combined with the absence of pharmacological agents that could modify the disease have highlighted the importance of prevention and early diagnosis of AD.

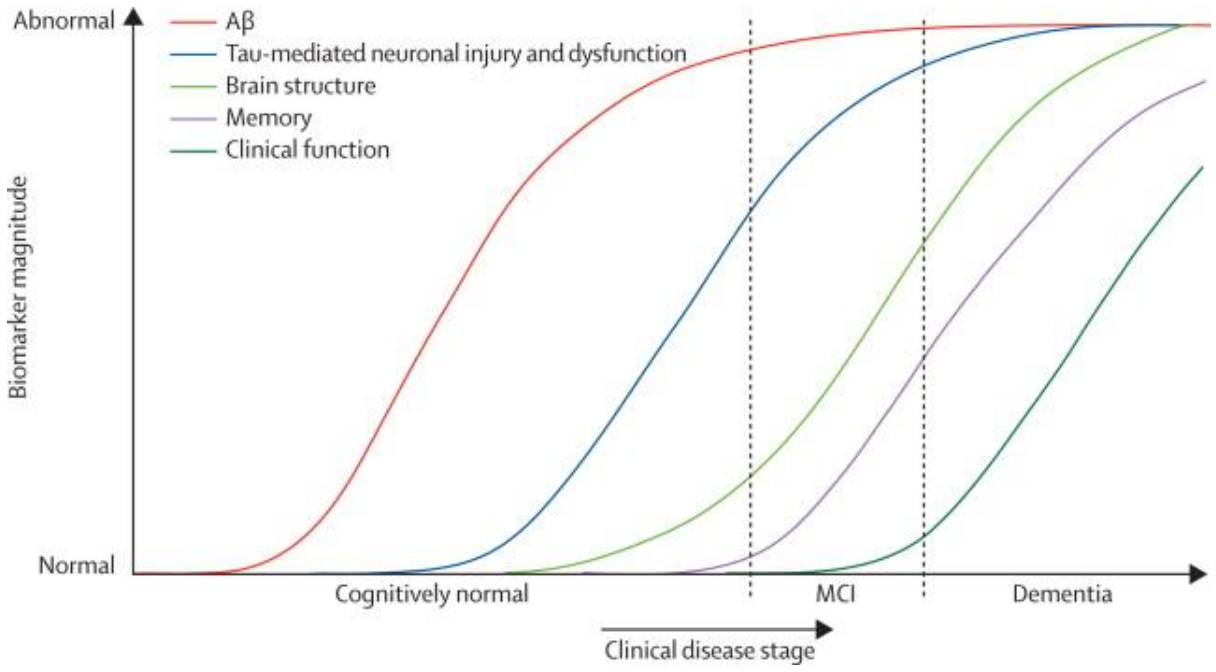

Figure 7.1 Hypothetical changes occurring before and after diagnosis of dementia (C. R. Jack, Jr. et al., 2013).

In this light, research focus has shifted to identifying individuals who are at higher risk of developing AD before significant pathological damage has taken place. One way of achieving this is through investigating people who express concerns about their memory. The subjective experience of memory worsening which is known as "Subjective Cognitive Decline" (SCD) has been suggested to occur at the pre-clinical stage of AD and constitute one possible indicator of future degeneration (Jessen et al., 2014).

However, people with SCD constitute a diverse group and when investigating the nature of such condition it is easier to think of it as a continuum that includes pre-dementia stage but also, personality characteristics, neurologic or psychiatric conditions, medication and substance use or even normal ageing (Jessen et al., 2014). It is imperative thus, to further understand this group and describe the traits of people with SCD.

7.1.2 Functional Cognitive Disorder

Another condition that is related to SCD, is Functional Cognitive Disorder (FCD). As mentioned earlier, FCD can be thought of as a subgroup of SCD because people who have received an FCD diagnosis have already visited a clinical setting due to memory complaints, but they do not have evidence of dementia.

Similarly to SCD, FCD is also an under-studied and diverse condition. It has been suggested that FCD is a form of functional neurological symptom disorder where symptoms are present but at the same time cannot be medically explained (Pennington, Hayre, et al., 2015). People with FCD experience memory lapses in their everyday life and such problems fluctuate with different levels of stress. When a person with FCD becomes aware of their memory lapses, they may experience fear and anger which in turn, heightens their stress levels and potentially leads to further memory failures (Pennington, Hayre, et al., 2015). In this chapter FCD patients have been included in the wider SCD group analysis.

7.1.3 Health Anxiety

Another notion that will be discussed in this chapter is Health Anxiety (HA). According to cognitive-behavioural theories, people with HA tend to misinterpret physical sensations and health related information (such as the results of medical examination) as indicators of a serious physical illness (Salkovskis et al., 2002). If some people experience high levels of HA as a result of misreading ambiguous information, then it is likely that people with severe HA are more prone to misinterpret ambiguous information. This association has led to the development of a validated tool that we used in this study, which measures HA and is sensitive to the whole spectrum of health-related concerns: from normal levels, up to clinical hypochondriasis (Salkovskis et al., 2002).

This questionnaire is named Health Anxiety Inventory (HAI) and was developed in 2002 by Salkovskis et al. (2002). The authors' main aim was to develop a tool that will measure HA in both medically ill

and healthy individuals. It consists of 18 items that measure the symptoms of HA (HA Total) and two additional sections: Avoidance and Reassurance. These additional sections measure whether people tend to avoid certain situations or not and how often they seek reassurance regarding their health from various sources. Both the Avoidance and Reassurance sections are scored independently and separately from the HA Total.

7.2 Objective

The main objective of this chapter is to investigate whether HA is related to the performance on cognitive testing and psychological questionnaires in people with SCD (and FCD). Due to the sample size and the fact that there is not literature on this relationship, I considered this to be an analysis of exploratory nature. The research question in this chapter is "Will people who have SCD/FCD and higher levels of HA perform worse on cognitive and psychological outcome measures, compared to people who have SCD/FCD and lower levels of HA?". The prediction is that they will.

7.3 Tasks and procedure

As described in the General Methods chapter, 100 people were tested at baseline, 90 SCD and 10 FCD. All participants were 45 years of age or older and were worried about their memory. Participants with FCD were recruited through a clinical setting (Cognitive Disorders Clinic at the Brain Centre, Southmead Hospital-North Bristol NHS Trust), while participants with SCD were recruited from public advertising, the Join Dementia Research service, our volunteer database (ReMemBr group) and one person from a Neurologist referral (see General Methods section for more detail).

All participants completed a Background questionnaire, cognitive testing and psychological questionnaires (see Appendix). More specifically, for cognitive testing we measured verbal memory (Rey Auditory Verbal Learning; RAVLT), verbal functioning (Letter and Semantic Fluency), working memory (N-back test), performance validity (Test of Memory Malingering; TOMM), visual attention and task switching (Trail Making Test A and B) and any memory impairment (Montreal Cognitive Assessment; MoCA). For the psychological outcome I assessed Health Anxiety (Health Anxiety Inventory), depression, anxiety and stress (Depression Anxiety and Stress scale; DASS), mindfulness (Five Facet Mindfulness Questionnaire; FFMQ) and self-reported levels of functional memory disorder (Functional Memory Disorder Questionnaire; FMDQ). Further information about the tests and questionnaires can be found in General Methods.

7.4 Results

7.4.1 Health Anxiety and Cognitive outcome measures

I performed Pearson's r and Spearman's rho correlations (for the MoCA, TOMM and Trail Making A and B tests that were not normally distributed), to examine the association between HA and cognitive function. The results suggested that three of the cognitive tests correlated significantly with the HAI measurements. In particular, the HAI Reassurance factor correlated with semantic fluency $r(99) = -.206$, $p<0.05$, two-tailed; Trail A $r(99) = +.317$, $p<0.01$, two-tailed and Trail B $r(99) = +.301$, $p<0.01$, two-tailed. Moreover, there was significant correlation between Trail A and HAI Total $r(99) = +.208$, $p<0.05$, two-tailed. These results should be interpreted with caution as this is an exploratory analysis. Moreover, multiple comparisons are likely to lead to significant findings due to chance. This applies to all analyses throughout this chapter. All correlations are depicted in Tables 7.1 and 7.2.

Table 7.1 Correlations between Health Anxiety and Cognitive outcome measures (Pearson's r scores)

	HAI Avoidance	HAI Reassurance	HAI Total
RAVLT	-.065	.003	.067
RAVLT LD	.109	-.075	-.077
Letter fluency	-.165	-.120	.031
Semantic fluency	.068	-.206*	-.162
N1 reaction time	.082	.112	.156
N1 accuracy	.034	-.150	-.094
N2 reaction time	.051	.009	.118
N2 accuracy	-.025	-.134	-.072
N3 reaction time	.045	-.088	.170
N3 accuracy	-.063	.039	.054

HAI= Health Anxiety Inventory (Avoidance, Reassurance and Total), RAVLT= Rey Auditory Verbal Learning Test, RAVLT LD= Rey Auditory Verbal Learning Test Long Delay, N1= N-back test for N=1, N2= N-back test for N=2, N3= N-back test for N=3 (reaction time and accuracy)

*p< 0.05 (2-tailed)

Table 7.2 Correlations between Health Anxiety and Cognitive outcome measures (Spearman's rho scores)

	HAI Avoidance	HAI Reassurance	HAI Total
MoCA	-.158	.069	.141
TOMM	-.082	.024	-.014
Trail A	-.015	.317**	.208*
Trail B	-.030	.301**	.057

HAI= Health Anxiety Inventory (Avoidance, Reassurance and Total), MoCA= Montreal Cognitive Assessment, TOMM= Test of Memory Malingering, Trail A and Trail B= Trail Making Test A and B

*p< 0.05 (2-tailed)

**p< 0.01 (2-tailed)

7.4.2 Health Anxiety and Psychological questionnaires

I also performed Pearson's r correlations, to examine the association between HA and psychological questionnaires. The results suggested that most of the questionnaires correlated strongly with HAI Avoidance and HAI Total. There were also three facets of the Five Facet Mindfulness questionnaire that correlated strongly with HAI Reassurance.

More specifically, HAI Avoidance correlated with FFMQ Observe $r(99)= - .237$, $p<0.05$, two-tailed; FFMQ Describe $r(99)= - .273$, $p<0.01$, two-tailed; FFMQ Act with awareness $r(99)= - .313$, $p<0.01$, two-tailed; FFMQ Non react $r(99)= - .261$, $p<0.01$, two-tailed.

Furthermore, HAI Avoidance also correlated with FMDQ Total $r(99)= + .368$, $p<0.01$, two-tailed; DASS Stress $r(99)= + .306$, $p<0.01$, two-tailed and DASS Total $r(99)= + .267$, $p<0.01$, two-tailed.

Additionally, I observed significantly strong correlations between HAI Total and FFMQ Act with awareness $r(99)= -.223$, $p<0.05$, two-tailed; FFMQ Non judge $r(99)= -.307$, $p<0.01$, two-tailed; DASS Depression $r(99)= +.250$, $p<0.05$, two-tailed; DASS Anxiety $r(99)= + .286$, $p<0.01$, two-tailed; DASS Stress $r(99)= + .226$, $p<0.05$, two-tailed; DASS Total $r(99)= + .294$, $p<0.01$, two-tailed and WHO-5 $r(99)= -.300$, $p<0.01$, two-tailed.

Lastly, HAI Reassurance correlated strongly with FFMQ Observe $r(99)= + .267$, $p<0.01$, two-tailed; FFMQ Act with awareness $r(99)= -.231$, $p<0.05$, two-tailed and FFMQ Non judge $r(99)= -.263$, $p<0.01$, two-tailed. All correlations are depicted in Table 7.3.

Table 7.3 Correlations between Health Anxiety and Psychological questionnaires

	HAI Avoidance	HAI Reassurance	HAI Total
FFMQ Observe	-.237*	.267**	.196
FFMQ Describe	-.273**	.017	.087
FFMQ Act	-.313**	-.231*	-.223*
FFMQ Non judge	-.015	-.263**	-.307**
FFMQ Non react	-.261**	.010	-.184
FMDQ Total	.368**	-.026	.002
DASS Depression	.184	.191	.250*
DASS Anxiety	.189	.136	.286**
DASS Stress	.306**	.078	.226*
DASS Total	.267**	.159	.294**
WHO-5	-.051	-.189	-.300**

HAI= Health Anxiety Inventory (Avoidance, Reassurance and Total), FFMQ= Five Facet Mindfulness questionnaire (Five facets: Observing, Describing, Acting with awareness, non-judging of inner experience and non-reactivity to inner experience), FMDQ= Functional Memory Disorder questionnaire, DASS= Depression, Anxiety and Stress scale, WHO= World health Organisation well-being questionnaire.

*p< 0.05 (2-tailed)

**p< 0.01 (2-tailed)

7.5 Discussion

7.5.1 Health Anxiety and Cognitive outcome measures

Correlational analyses were used to examine the relationship between the HA measures and measurements of cognitive functions in people with SCD and FCD. To our knowledge, there is no relevant literature available as no one has investigated this association so far but according to the research question we would expect people who have SCD/FCD and higher levels of HA to score lower on the cognitive tests.

Results indicated a reverse relationship between semantic fluency and HAI Reassurance, meaning that people who sought more reassurance had a lower score on the semantic fluency task. This finding is new and quite interesting, but it could possibly be due to chance and requires replication.

A higher score on the HAI Reassurance scale would mean that an individual is more anxious. The HAI Reassurance measurement was also strongly linked to Trail A and Trail B. Similarly, a higher score on the HAI Reassurance scale would suggest a more anxious individual who is taking longer time to complete the cognitive tasks. Lastly, Trail A was also associated with HAI Total score, meaning that there is a strong link between HAI and visual attention, visual motor speed, visual scanning and sequencing. This finding is again in line with this chapter's expectation, but such results should again be interpreted with caution. In addition to that, all the above results would require to be replicated with a bigger sample and would need further examination as the HAI Total score was not strongly associated with the rest of the cognitive measures.

7.5.2 Health Anxiety and Psychological questionnaires

More relationships were observed between HA and other psychological variables in people with SCD and FCD. Contrary to the cognitive tasks, we observed more relationships between the HAI and psychological measures.

More specifically, I examined the relationships between all the facets of Mindfulness and HA. People who are more prone to notice their experiences, sensations, emotions and cognitions (Observe), label their thoughts and feelings with words (Describe), allow them to come and go without getting caught up (Non react) and generally behave with more awareness (Act), tended to score lower on the HAI Avoidance scale. The measurements of not judging oneself and acting with more awareness were also negatively linked to the rest of HA scales (HAI Reassurance and HAI Total) leading to the conclusion that indeed, people who are less anxious about their health would take a more non-evaluative stance towards their thoughts and experiences and would behave less mechanically.

These findings are in accordance with previous studies that have investigated the effectiveness of Mindfulness Based Cognitive Therapy (MBCT) in people with severe HA. One pilot study showed that an 8-week mindfulness intervention helped participants decrease their HA symptoms and sustained

such results for at least 3 months (Lovas & Barsky, 2010). Additionally, another study that examined MBCT as a treatment method for HA, concluded that most participants were benefited from an MBCT course. In more detail, they were more able to relax and be less anxious in various situations, improved their mood and sleep, were more able to cope with everyday struggles and took on a more accepting attitude towards life post-intervention (Williams, McManus, Muse, & Williams, 2011). However, these finding refer to Mindfulness as an intervention rather than a trait. In this study I measured how mindful participants were at baseline before any intervention took place but such association between aspects of mindfulness and HA can be promising for the development of future interventions, tailored to the needs of SCD and FCD populations.

Another interesting finding was that people with more HAI Avoidance were more likely to report functional memory disorder symptoms (FMDQ questionnaire). This could be explained by the fact that people with FCD are more likely to have experienced a stressful life event (Pennington, Newson, et al., 2015). However, this is just a speculation as there is no evidence about the relationship between FCD and HA in particular.

Furthermore, I observed a significant relationship between HAI Avoidance and HAI Total scores and depression, anxiety and stress. This led to the conclusion that participants who were more likely to be stressed tend to avoid HA triggers and more generally, participants who had higher levels of depression, anxiety and stress tended to be more anxious about their health. Again, despite the absence of literature this is an expected finding as we would anticipate HA to affect mood and anxiety/stress levels in general.

Lastly, participants who were more health anxious reported a lower level of well-being. This is the first time to my knowledge that well-being has been associated with HA in SCD and FCD population and just like the previous findings above, this could be a good start to further describe the characteristics of this sample and better understand the conditions. A more detailed documentation of SCD and FCD traits could ultimately lead researchers to tailor interventions to promote brain health and well-being in these individuals.

Chapter 8 General Discussion

The aims of this thesis were twofold. Firstly, to better understand people with Subjective Cognitive Decline (SCD) and, secondly, to examine whether two different interventions could potentially improve their cognition and psychological state. SCD has attracted a lot of interest due to the hypothesis that it might constitute a pre-clinical stage of Alzheimer's disease (AD) (Jessen et al., 2014). Since AD is a progressive neurodegenerative disease and currently has no treatment to stop the progression of it, it is of vital importance to identify it at the earliest stage possible. It is also important to investigate what sorts of interventions could have the maximum effectiveness at this stage, before major neurodegeneration occurs. For this reason, I developed a new intervention based on lifestyle factors that have been suggested to improve and protect brain health. The intention was not only to examine the effectiveness of such intervention, but also to compare it against an already existing intervention that has started to gain popularity in the field of Psychology and Neurosciences, that is Mindfulness Meditation.

Moreover, SCD constitutes a common symptom that has been associated with normal ageing, personality, psychiatric and psychological conditions (Jessen et al., 2014). It is a very diverse group that has not yet been fully understood and has provoked a lot of debate around its definition and management (Tales et al., 2015a). In order to cover the scope of this thesis, I described the characteristics of people with SCD and FCD that were recruited for this study. In addition to that, I talked about their ApoE genotype, examined the relationship between their cognitive and psychological performance and Health anxiety and investigated their Readiness to change and actual behavioural changes after the interventions. Lastly, I compared this sample of people with SCD to a smaller sample of people with Functional Cognitive Disorder (FCD) who also participated in the DECODE study.

There is one important thing that needs to be mentioned before interpreting the results of this study. Throughout this thesis I have examined two specific groups of people with SCD and FCD. Both of these conditions remain understudied but have the common ground of self-reported memory complaints and they both have been associated with a higher risk of future dementia. However, since their aetiology remains unknown it is of critical importance to highlight that SCD and FCD might indeed constitute a pre-dementia indicator, but they are also broader than that. We should not ignore the fact that they are heterogeneous conditions that can be placed on a spectrum from normal ageing, to early neurodegeneration. At the same time, there are many other possible explanations, like the possibility of underlying psychological factors. Consequently, when interpreting the following findings, I would like for readers to keep in mind that the possibility of SCD and FCD indicating early neurodegeneration is only one approach to the attempt of understanding such broad diagnostic entities.

8.1 Conclusions and original contribution of thesis

Chapter 3 was a description of the study sample, which included people with SCD and people with FCD. Most of them were highly educated women who were already exercising. Additionally, half of the participants in the SCD group had a family history of dementia or AD which is something that has been reported in a previous study (Clarnette et al., 2001). This finding is quite interesting as it could potentially be another factor that contributed to worrying about memory decline. This is only a speculation, but I found quite intriguing the fact that many of the participants in the initial interview, expressed their interest in research and prevention of dementia, because they had seen a loved one suffering from the disease. Another interesting observation is that most of the sample (SCD and FCD combined), tended to be over-weight but healthy individuals with a history of depression (40%). It has been previously reported that depressive symptoms could be prodromal to cognitive decline (Berger, Fratiglioni, Forsell, Winblad, & Backman, 1999) but this has not been confirmed. Even though causality cannot be assumed, it is important to highlight the relationship between SCD and depression and see it as a starting point for further investigation.

Moving on to the cognitive and psychological scores of the sample, I compared it against the normative data available, in order to investigate their similarity to the general population. Both SCD and FCD groups scored closely to average, with the only exception of the Rey Auditory Verbal Learning test (RAVLT). This finding supports merely the concept that it is hard to identify people with SCD as they usually score within the normal limits. However, their lower than average scores on RAVLT provide at the same time a starting point to further examine the sensitivity of this test, as tool that could help to early identify people at risk of dementia.

Additionally, the aim of Chapter 3 was to discuss FCD in more detail and examine its association with SCD. The two conditions had a few differences. FCD patients tended to be more overweight, meditate more and visit their GP more often, compared to SCD participants. Another difference was that SCD participants were more likely to have family history of dementia or AD. After comparing the two groups against the psychological outcome measures, I observed that people with FCD tended to have a higher rate of failure on the performance validity test (TOMM), compared to the SCD group. It is notable that the TOMM (or any other performance validity test) is very rarely used in any research looking at SCD, MCI or dementia. Consequently, it would be a very useful test when looking at SCD, FCD and MCI and trying to identify people at risk of developing dementia.

Chapter 4 investigated the effectiveness of two interventions on a sample of people with SCD. More specifically, I examined whether two online courses (Mindfulness meditation and Lifestyle factors training) could improve their cognitive function and psychological well-being. As Mindfulness has been suggested to reduce stress, anxiety and depression (Kabat-Zinn, 1982; Kabat-Zinn et al., 1992), I hypothesised that Mindfulness training could potentially improve the psychological state of the

participants. In addition to that, some studies have shown that Mindfulness might also improve participants' performance on cognitive tasks (Moore & Malinowski, 2009; Zeidan et al., 2010). Consequently, one of the hypotheses in Chapter 4 was that people who attended an online course on Mindfulness training would perform better on the cognitive tests and psychological questionnaires.

The second hypothesis in Chapter 4 was that people who attended the course on modifiable lifestyle factors, would also benefit from it and report higher cognitive and psychological scores. The Lifestyle factors intervention was developed for the purposes of this study and was based on previous studies like the Caerphilly (Elwood et al., 1999a) and the FINGER study (T. Ngandu et al., 2015). Researchers in these studies showed that factors like exercise, diet and sleep might help people maintain their cognition. The main idea behind it was to encourage people towards a healthier way of living and to engage with activities that would keep them happy and socially and mentally engaged. Both interventions lasted for 4 weeks and were compared against each other and against a Control group. All participants attended a baseline visit, a visit after the end of the interventions and finally, a 6 months follow-up.

However, contrary to the predictions none of the groups did any better on the cognitive tests but, people in the Mindfulness group reported a better well-being compared to the other groups. Even though this effect was not maintained at the 6 months follow-up, it confirms the hypothesis that Mindfulness can improve well-being in people with SCD. If this finding is replicated with a bigger sample, it could help researchers design tailored interventions in the future. Such interventions would not only help the community intervene at an early stage of neurodegeneration but, would also be relieving for people with SCD, no matter if they carry on developing AD or not. Experiencing such symptoms of memory lapses, in the absence of objective impairment on examination, can lead people in this group to feel frustration and become even more concerned and stressed about their memory in the future. The fact that there will be something to offer to them and possibly relieve their symptoms would be an important step towards managing such a condition.

Throughout Chapter 5, I took a speculative approach rather than interpreting the statistical analyses. This was because I had to divide the three intervention groups into Changers (people willing to change) and No-changers (people who did not intend to change). However, many people who were already at the stage of a change had to be excluded, leaving each group with a very small sample. An observation of the data showed that No-Changers were more likely to be overweight. Moreover, the Lifestyle group was the one where participants were asked to perform a 15-minute brisk walk at least three times per week. Consequently, this was the group where we would expect Changers to significantly increase their amount of exercise, compared to No-changers. However, both groups increased their brisk walking and Changers kept increasing it up to the 6 months follow-up, while No-changers didn't (this finding was not significant). Despite not being able to draw any reliable conclusions from such a small sample it is worth examining the effectiveness of such intervention in the future, with a bigger sample.

Another outcome of this thesis was the finding that participants who carried at least one copy of the ApoE4 tended to be slower than non-carriers on the working memory task, while E2 carriers were faster than non-carriers (Chapter 6). Since the E4 allele has been linked with higher risk of cognitive decline and the E2 is thought to play a protective role against dementia, it would be useful to examine the relationship between the ApoE gene and cognitive performance in SCD. In addition to that, E4 carriers in this study reported higher levels of stress and depression and lower levels of well-being. This finding is in accordance with a previous study (Skoog et al., 2015) and adds to the effort of examining whether people with SCD, who are also E4 carriers are more prone to depression and, how this might affect their risk of developing dementia.

The following chapter (Chapter 7), investigated the relationship of Health Anxiety with cognitive performance and psychological state, in people with SCD and FCD. This work suggested that there is a link between Health Anxiety and Mindfulness, depression, anxiety, stress and well-being. Particularly, it showed that people who were less anxious about their health were less likely to be on auto-pilot and would be more aware of their emotions and thoughts. Moreover, the less health anxious they were, the less depressed, anxious and stressed they would feel, and would be more likely to report better well-being. These findings confirm previous studies suggesting that a mindfulness intervention helped participants reduce their health anxiety (Kabat-Zinn et al., 1992). What this thesis' work adds to these findings though, is that in this chapter, mindfulness was measured as a personality trait rather than an intervention outcome. Consequently, the findings suggest that in order to design a successful intervention for people with SCD, we should also consider how mindful they are prior to any intervention and how this could affect their levels of health anxiety that could also include worrying about memory.

8.2 Limitations

One of the main issues with this work is the absence of standard criteria for the identification of SCD. The fact that SCD has not yet been fully defined, makes it hard for studies to use the same recruitment criteria. We identified participants with SCD by asking them if they were concerned that their memory and thinking are declining and, if such decline was more than normal ageing (Smart et al., 2014). These criteria are likely to ignore other aspects of the SCD profile, such as Health Anxiety levels or any potential psychological symptoms such as depression or stress. I believe that there is a need for more specific criteria to define more homogeneous samples of SCD for research. In this way it will be easier to examine separately the different SCD subtypes, like people who might progress to MCI and dementia, and people whose memory concerns are of psychological aetiology.

Another limitation of this study is the selection bias. The sample was probably not representative of a random sample of people with SCD. It is easy to observe that at the baseline visit, the average amount

of exercise and average years of education were both quite high. Furthermore, a big percentage of them had a family history of dementia or AD and some of them had already signed up as volunteers on a research database. Interpreting these observations could lead to the conclusion that participants were already very aware of dementia and AD and had been living a healthy lifestyle. The long education along with the family history of dementia and AD, could potentially have led them to research dementia and do all the things that researchers are suggesting that are good for the brain. In the future, it would be preferable if participants are recruited from a wider variety of pathways and perhaps correct for variables like education level.

Furthermore, another issue is that compliance with the Interventions could not be measured. The commercially available Mindfulness course could not provide us with data on each participant. In the Lifestyle group, we did ask people to report the amount of brisk walking they were doing everyday but, this was a self-reported measure. Self-reports are not very reliable, and it would be better if such variable could be measured objectively, by using devices like fit bit.

A problem that applied to several chapters was the size of the sample. It was quite hard to recruit people with FCD and unfortunately, many of them dropped out during the study. This made it hard to maintain numbers that could be compared against the SCD group and would be big enough for statistical analyses. It is important to keep in mind when interpreting the results, that findings regarding such small subgroups (N=10) cannot be generalised for a whole clinical population. They could however, constitute a starting point for further investigation and follow-up.

In addition to that, a larger SCD sample would also be very helpful when dividing people into the intervention groups or in reference to other variables, like their genotype, Health anxiety or Readiness to change.

Lastly, I realise it would have been useful to have considered a broader range of factors influencing memory and cognition in mid-life. Unfortunately, I have not acquired such information but, this would help a lot in better characterising the SCD group in the future. I will consider applying these criteria in a future study or perhaps if I get the chance to follow-up this sample.

Some of the analyses in this thesis were of exploratory nature. The results should therefore be interpreted with caution. Lastly, it is important to note that when performing multiple comparisons, there is always the possibility of having significant findings by chance.

8.3 Future directions

One of this work's findings was that Mindfulness meditation as an intervention can increase the well-being of people with SCD. One way to support this would be by recruiting people with different SCD

subtypes. Moreover, by measuring the compliance with the Mindfulness course in an objective and reliable way and by encouraging participants to keep practicing, researchers could possibly validate such results. Further to that, organising visits that are closer than 6 months apart could be another way to make an intervention successful, as it would likely maintain participants' momentum and motivation.

If such findings are confirmed, then researchers could move on to design interventions that are tailored to the SCD population. This would suggest considering how mindful a person already is and whether they have high levels of health anxiety or not. In this way, the more personalised the intervention is, the more likely it will be to reach its full potential.

Furthermore, the relationship between the ApoE gene and depression in SCD should be examined further. The link between these three variables is not clear yet, but there seems to be an association between all of them. One way to investigate this, would be to identify E4 carriers and non-carriers with SCD and follow them longitudinally. Measuring their levels of depression at each time point, along with their cognitive function, would enable researchers to examine who went on to develop dementia and who didn't and whether depression and E4 carriage were additional risk factors in people with SCD.

Moreover, it is quite interesting that the ApoE4 gene was associated with lower working memory but not lower RAVLT, whereas SCD was associated with lower RAVLT but not working memory. One possible explanation could be that lower RAVLT is related to "self-fulfilling prophecy" or "diagnosis threat" (Suhr & Gunstad, 2005). All of the participants knew they were in the study because of memory concerns, so that might have affected their RAVLT performance (they performed poorly, as they were expected to).

One study showed that among students who had previous head injury, participants would perform more poorly on cognitive tests if attention was drawn to the fact that they had had a head injury (compared to those who were not reminded of this fact) (Suhr & Gunstad, 2005). Something similar perhaps could have happened with the SCD participants of this study. That is, maybe they performed poorly on RAVLT because they are in a study for people with memory concerns. One way to investigate this in the future could be to get a large random sample of older people, give them several tests and questionnaires and then look at the relationship between memory concerns and RAVLT. Would RAVLT still be lower in the people with memory concerns if they don't think they are in the study because they have memory concerns?

Unfortunately, we did not measure compliance for the Mindfulness group, as there was not a standard amount of practising time proposed in the online course. In the future, it would be useful to measure compliance for different types of interventions in an objective way, instead of self-reports.

It has been discussed in this thesis that more research is needed in order to establish the variables that are related to the risk of developing dementia. One way forward would be to further examine the predictive value of working memory tests in this population.

An interesting finding of this study was the difference between the SCD and FCD groups on the TOMM test. FCD patients were more likely to fail this test in comparison to people with SCD. This is worth of more investigation as TOMM could be an important tool when trying to identify people with a higher risk of dementia.

8.4 Conclusions

In summary, this study managed to describe the characteristics of participants with SCD and FCD, evaluated the effectiveness of two interventions and suggested a starting point for future research into tests that could possibly help us identify people at risk of dementia.

One thing that could be done differently, would be the tool used for documenting lifestyle variables over time. I have not included this information in the thesis because the tool I used was not standardised. This resulted into a lot of data (some of them qualitative, like the kind of mentally and socially stimulating activities the participants engaged in), that were hard to be analysed within the appropriate timeline.

If I could do this research all over again, I would choose a standardised way of collecting these data, as they could contribute to the examination of lifestyle habits in the SCD population.

Finally, as researchers and clinicians are currently working towards the prevention and early detection of dementia, I am hoping that this study could constitute a fertile ground for future investigation.

References

Alzheimer's, A. (2015). 2015 Alzheimer's disease facts and figures. *Alzheimer's & dementia: the journal of the Alzheimer's Association, 11*(3), 332.

Abramowitz, J. S., & Braddock, A. E. (2008). *Psychological treatment of health anxiety and hypochondriasis : a biopsychosocial approach*. Gottingen, Germany: Hogrefe & Huber Publishers.

Abramowitz, J. S., & Moore, E. L. (2007). An experimental analysis of hypochondriasis. *Behav Res Ther, 45*(3), 413-424. doi:10.1016/j.brat.2006.04.005

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Ali, J. I., Smart, C. M., & Gawryluk, J. R. (2018). Subjective Cognitive Decline and APOE varepsilon4: A Systematic Review. *J Alzheimers Dis, 65*(1), 303-320. doi:10.3233/JAD-180248

Almeida, O. P., Hill, K., Howard, R., Obrien, J., & Levy, R. (1993). Demographic and Clinical-Features of Patients Attending a Memory Clinic. *International Journal of Geriatric Psychiatry, 8*(6), 497-501. doi:DOI 10.1002/gps.930080607

Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Peres, K., Barberger-Gateau, P., . . . Dartigues, J. F. (2008). Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Ann Neurol, 64*(5), 492-498. doi:10.1002/ana.21509

Asmundson, G. J., Abramowitz, J. S., Richter, A. A., & Whedon, M. (2010). Health anxiety: current perspectives and future directions. *Curr Psychiatry Rep, 12*(4), 306-312. doi:10.1007/s11920-010-0123-9

Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology-Science and Practice, 10*(2), 125-143. doi:10.1093/clipsy/bpg015

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment, 13*(1), 27-45. doi:10.1177/1073191105283504

Baer, R. A., Smith, G. T., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., . . . Williams, J. M. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment, 15*(3), 329-342. doi:10.1177/1073191107313003

Balash, Y., Mordechovich, M., Shabtai, H., Giladi, N., Gurevich, T., & Korczyn, A. D. (2013). Subjective memory complaints in elders: depression, anxiety, or cognitive decline? *Acta Neurol Scand, 127*(5), 344-350. doi:10.1111/ane.12038

Bassuk, S. S., Glass, T. A., & Berkman, L. F. (1999). Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Annals of Internal Medicine, 131*(3), 165-173. doi:10.7326/0003-4819-131-3-199908030-00002

Bech, P., Olsen, L. R., Kjoller, M., & Rasmussen, N. K. (2003). Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. *Int J Methods Psychiatr Res, 12*(2), 85-91.

Berger, A. K., Fratiglioni, L., Forsell, Y., Winblad, B., & Backman, L. (1999). The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology, 53*(9), 1998-2002. doi:10.1212/wnl.53.9.1998

Berrios, G. E., & Hodges, J. R. (2000). *Memory disorders in psychiatric practice*. Cambridge, UK ; New York, NY: Cambridge University Press.

Bertram, L., McQueen, M. B., Mullin, K., Blacker, D., & Tanzi, R. E. (2007). Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet, 39*(1), 17-23. doi:10.1038/ng1934

Bialystok, E., Craik, F. I., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia, 45*(2), 459-464. doi:10.1016/j.neuropsychologia.2006.10.009

Bialystok, E., Craik, F. I., Klein, R., & Viswanathan, M. (2004). Bilingualism, aging, and cognitive control: evidence from the Simon task. *Psychol Aging, 19*(2), 290-303. doi:10.1037/0882-7974.19.2.290

Bohlmeijer, E., ten Klooster, P. M., Fledderus, M., Veehof, M., & Baer, R. (2011). Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment, 18*(3), 308-320. doi:10.1177/1073191111408231

Borland, E., Nagga, K., Nilsson, P. M., Minthon, L., Nilsson, E. D., & Palmqvist, S. (2017). The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort. *J Alzheimers Dis, 59*(3), 893-901. doi:10.3233/JAD-170203

Breteler, M. M. B. (2000). Vascular risk factors for Alzheimer's disease: An epidemiologic perspective. *Neurobiology of aging, 21*(2), 153-160. doi:Doi 10.1016/S0197-4580(99)00110-4

Brown, H. D., Kosslyn, S. M., Delamater, B., Fama, J., & Barsky, A. J. (1999). Perceptual and memory biases for health-related information in hypochondriacal individuals. *J Psychosom Res, 47*(1), 67-78. doi:10.1016/s0022-3999(99)00011-2

Brown, K. W., Ryan, R. A., & Creswell, J. D. (2007). Mindfulness: Theoretical foundations and evidence for its salutary effects. *Psychological Inquiry, 18*(4), 211-237. doi:Doi 10.1080/10478400701598298

Cao, C. H., Loewensteine, D. A., Lin, X. Y., Zhang, C., Wang, L., Duara, R., . . . Arendash, G. W. (2012). High Blood Caffeine Levels in MCI Linked to Lack of Progression to Dementia. *Journal of Alzheimers Disease, 30*(3), 559-572. doi:10.3233/Jad-2012-111781

Carlson, M. C., Erickson, K. I., Kramer, A. F., Voss, M. W., Bolea, N., Mielke, M., . . . Fried, L. P. (2009). Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. *J Gerontol A Biol Sci Med Sci, 64*(12), 1275-1282. doi:10.1093/gerona/glp117

Clarnette, R. M., Almeida, O. P., Forstl, H., Paton, A., & Martins, R. N. (2001). Clinical characteristics of individuals with subjective memory loss in Western Australia: Results from a cross-sectional survey. *International Journal of Geriatric Psychiatry, 16*(2), 168-174. doi:Doi 10.1002/1099-1166(200102)16:2<168::Aid-Gps291>3.0.Co;2-D

Corder, E. H., Saunders, A. M., Risch, N. J., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Jr., . . . et al. (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet, 7*(2), 180-184. doi:10.1038/ng0694-180

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., . . . Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921-923.

Cosentino, S., Scarmeas, N., Helzner, E., Glymour, M. M., Brandt, J., Albert, M., . . . Stern, Y. (2008). APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. *Neurology, 70*(19 Pt 2), 1842-1849. doi:10.1212/01.wnl.0000304038.37421.cc

Crawford, J. R., Garthwaite, P. H., Lawrie, C. J., Henry, J. D., MacDonald, M. A., Sutherland, J., & Sinha, P. (2009). A convenient method of obtaining percentile norms and accompanying interval estimates for self-report mood scales (DASS, DASS-21, HADS, PANAS, and sAD). *Br J Clin Psychol, 48*(Pt 2), 163-180. doi:10.1348/014466508X377757

Crichton, G. E., Bryan, J., & Murphy, K. J. (2013). Dietary Antioxidants, Cognitive Function and Dementia - A Systematic Review. *Plant Foods for Human Nutrition, 68*(3), 279-292. doi:10.1007/s11130-013-0370-0

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., . . . Starr, J. M. (2009). Age-associated cognitive decline. *Br Med Bull, 92*, 135-152. doi:10.1093/bmb/ldp033

Deng, J., Zhou, D. H., Li, J., Wang, Y. J., Gao, C., & Chen, M. (2006). A 2-year follow-up study of alcohol consumption and risk of dementia. *Clin Neurol Neurosurg, 108*(4), 378-383. doi:10.1016/j.clineuro.2005.06.005

Detert, N. B. (2015). Mindfulness for neurologists. *Pract Neurol, 15*(5), 369-374. doi:10.1136/practneurol-2015-001100

Dik, M. G., Jonker, C., Comijs, H. C., Bouter, L. M., Twisk, J. W., van Kamp, G. J., & Deeg, D. J. (2001). Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology, 57*(12), 2217-2222. doi:10.1212/wnl.57.12.2217

Duman, B. S., Ozturk, M., Yilmazer, S., & Hatemi, H. (2004). Apolipoprotein E polymorphism in Turkish subjects with Type 2 diabetes mellitus: allele frequency and relation to serum lipid concentrations. *Diabetes Nutr Metab, 17*(5), 267-274.

Elwood, P. C., Gallacher, J. E., Hopkinson, C. A., Pickering, J., Rabbitt, P., Stollery, B., . . . Bayer, A. (1999a). Smoking, drinking, and other life style factors and cognitive function in men in the Caerphilly cohort. *J Epidemiol Community Health, 53*(1), 9-14.

Elwood, P. C., Gallacher, J. E. J., Hopkinson, C. A., Pickering, J., Rabbitt, P., Stollery, B., . . . Bayer, A. (1999b). Smoking, drinking, and other life style factors and cognitive function in men in the Caerphilly cohort. *Journal of Epidemiology and Community Health, 53*(1), 9-14. doi:DOI 10.1136/jech.53.1.9

Estevez-Gonzalez, A., Kulisevsky, J., Boltes, A., Otermin, P., & Garcia-Sanchez, C. (2003). Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: comparison with mild cognitive impairment and normal aging. *Int J Geriatr Psychiatry, 18*(11), 1021-1028. doi:10.1002/gps.1010

Farlow, M. R., He, Y., Tekin, S., Xu, J., Lane, R., & Charles, H. C. (2004). Impact of APOE in mild cognitive impairment. *Neurology, 63*(10), 1898-1901.

Farrer, L. A., Cupples, L. A., van Duijn, C. M., Kurz, A., Zimmer, R., Muller, U., . . . et al. (1995). Apolipoprotein E genotype in patients with Alzheimer's disease: implications for the risk of dementia among relatives. *Ann Neurol, 38*(5), 797-808. doi:10.1002/ana.410380515

Fernandez, A., Goldberg, E., & Michelon, P. . (2013). *The SharpBrains guide to brain fitness: How to optimize brain health and performance at any age. SharpBrains.*

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet, 355*(9212), 1315-1319. doi:10.1016/S0140-6736(00)02113-9

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *J Neurosci, 23*(27), 9240-9245.

Geerlings, M. I., Jonker, C., Bouter, L. M., Ader, H. J., & Schmand, B. (1999). Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am J Psychiatry, 156*(4), 531-537. doi:10.1176/ajp.156.4.531

Geffen, G. M., Butterworth, P., & Geffen, L. B. (1994). Test-retest reliability of a new form of the auditory verbal learning test (AVLT). *Arch Clin Neuropsychol, 9*(4), 303-316.

Gladsjo, J. A., Schuman, C. C., Evans, J. D., Peavy, G. M., Miller, S. W., & Heaton, R. K. (1999). Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment, 6*(2), 147-178. doi:10.1177/107319119900600204

Grossman, P., Niemann, L., Schmidt, S., & Walach, H. (2004). Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res, 57*(1), 35-43. doi:10.1016/S0022-3999(03)00573-7

Hambrick, D. Z., Salthouse, T. A., & Meinz, E. J. (1999). Predictors of crossword puzzle proficiency and moderators of age-cognition relations. *Journal of Experimental Psychology-General, 128*(2), 131-164.

Hampel, H., Burger, K., Pruessner, J. C., Zinkowski, R., DeBernardis, J., Kerkman, D., . . . Teipel, S. J. (2005). Correlation of cerebrospinal fluid levels of Tau protein phosphorylated at threonine 231 with rates of hippocampal atrophy in Alzheimer disease. *Archives of neurology, 62*(5), 770-773. doi:DOI 10.1001/archneur.62.5.770

Hanna-Pladdy, B., & MacKay, A. (2011). The relation between instrumental musical activity and cognitive aging. *Neuropsychology, 25*(3), 378-386. doi:10.1037/a0021895

Harwood, D. G., Barker, W. W., Ownby, R. L., Mullan, M., & Duara, R. (2004). No association between subjective memory complaints and apolipoprotein E genotype in cognitively intact elderly. *Int J Geriatr Psychiatry, 19*(12), 1131-1139. doi:10.1002/gps.1193

Heffernan, A. L., Chidgey, C., Peng, P., Masters, C. L., & Roberts, B. R. (2016). The Neurobiology and Age-Related Prevalence of the epsilon4 Allele of Apolipoprotein E in Alzheimer's Disease Cohorts. *J Mol Neurosci, 60*(3), 316-324. doi:10.1007/s12031-016-0804-x

Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol, 44*(Pt 2), 227-239. doi:10.1348/014466505X29657

Heron, M. (2016). Deaths: Leading Causes for 2014. *Natl Vital Stat Rep, 65*(5), 1-96.

Hessen, E., Eckerstrom, M., Nordlund, A., Selseth Almdahl, I., Stalhammar, J., Bjerke, M., . . . Wallin, A. (2017). Subjective Cognitive Impairment Is a Predominantly Benign Condition in Memory Clinic Patients Followed for 6 Years: The Gothenburg-Oslo MCI Study. *Dement Geriatr Cogn Dis Extra, 7*(1), 1-14. doi:10.1159/000454676

Hoogenhout, E. M., de Groot, R. H., van der Elst, W., & Jolles, J. (2012). Effects of a comprehensive educational group intervention in older women with cognitive complaints: a randomized controlled trial. *Aging Ment Health, 16*(2), 135-144. doi:10.1080/13607863.2011.598846

Hurt, C. S., Burns, A., Brown, R. G., & Barrowclough, C. (2012). Why don't older adults with subjective memory complaints seek help? *Int J Geriatr Psychiatry, 27*(4), 394-400. doi:10.1002/gps.2731

Jack, C. R. (2012). Alzheimer Disease: New Concepts on Its Neurobiology and the Clinical Role Imaging Will Play. *Radiology, 263*(2), 343-360. doi:10.1148/radiol.12110433

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., . . . Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol, 12*(2), 207-216. doi:10.1016/S1474-4422(12)70291-0

Jack, C. R., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology, 9*(1), 119-128. doi:Doi 10.1016/S1474-4422(09)70299-6

Jenkins, A., Tree, J. J., Thornton, I. M., & Tales, A. (2019). Subjective Cognitive Impairment in 55-65-Year-Old Adults Is Associated with Negative Affective Symptoms, Neuroticism, and Poor Quality of Life. *J Alzheimers Dis, 67*(4), 1367-1378. doi:10.3233/JAD-180810

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., . . . Wagner, M. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol, 19*(3), 271-278. doi:10.1016/S1474-4422(19)30368-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chetelat, G., . . . Grp, S. I. W. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers & Dementia, 10*(6), 844-852. doi:10.1016/j.jalz.2014.01.001

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kolsch, H., . . . Dementia in Primary Care Patients Study, G. (2010). Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry, 67*(4), 414-422. doi:10.1001/archgenpsychiatry.2010.30

Jorm, A. F., Christensen, H., Korten, A. E., Henderson, A. S., Jacomb, P. A., & Mackinnon, A. (1997). Do cognitive complaints either predict future cognitive decline or reflect past cognitive decline? A longitudinal study of an elderly community sample. *Psychological Medicine, 27*(1), 91-98. doi:Doi 10.1017/S0033291796003923

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry, 4*(1), 33-47.

Kabat-Zinn, J., Massion, A. O., Kristeller, J., Peterson, L. G., Fletcher, K. E., Pbert, L., . . . Santorelli, S. F. (1992). Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry, 149*(7), 936-943. doi:10.1176/ajp.149.7.936

Kalmijn, S., Feskens, E. J. M., Launer, L. J., & Kromhout, D. (1997). Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *American Journal of Epidemiology, 145*(1), 33-41.

Kang, J. H., Ascherio, A., & Grodstein, F. (2005). Fruit and vegetable consumption and cognitive decline in aging women. *Annals of Neurology, 57*(5), 713-720. doi:10.1002/ana.20476

Kawachi, I., & Berkman, L. F. (2001). Social ties and mental health. *J Urban Health, 78*(3), 458-467. doi:10.1093/jurban/78.3.458

Keage, H. A., Banks, S., Yang, K. L., Morgan, K., Brayne, C., & Matthews, F. E. (2012). What sleep characteristics predict cognitive decline in the elderly? *Sleep Med, 13*(7), 886-892. doi:10.1016/j.sleep.2012.02.003

Krikorian, R., Shidler, M. D., Nash, T. A., Kalt, W., Vinqvist-Tymchuk, M. R., Shukitt-Hale, B., & Joseph, J. A. (2010). Blueberry Supplementation Improves Memory in Older Adults. *Journal of Agricultural and Food Chemistry, 58*(7), 3996-4000. doi:10.1021/jf9029332

Krishnan, K. R., Tupler, L. A., Ritchie, J. C., Jr., McDonald, W. M., Knight, D. L., Nemeroff, C. B., & Carroll, B. J. (1996). Apolipoprotein E-epsilon 4 frequency in geriatric depression. *Biol Psychiatry, 40*(1), 69-71. doi:10.1016/0006-3223(95)00424-6

Kristeller, J. L., & Hallett, C. B. (1999). An Exploratory Study of a Meditation-based Intervention for Binge Eating Disorder. *Journal of Health Psychology, 4*(3), 357-363. doi:10.1177/135910539900400305

Krueger, K. R., Wilson, R. S., Kamenetsky, J. M., Barnes, L. L., Bienias, J. L., & Bennett, D. A. (2009). Social engagement and cognitive function in old age. *Exp Aging Res, 35*(1), 45-60. doi:10.1080/03610730802545028

Krusche, A., Cyhlarova, E., King, S., & Williams, J. M. (2012). Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. *BMJ Open, 2*(3). doi:10.1136/bmjopen-2011-000803

Krusche, A., Cyhlarova, E., King, S., & Williams, J. M. G. (2012). Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. *BMJ Open, 2*(3). doi:ARTN e000803

10.1136/bmjopen-2011-000803

Krusche, A., Cyhlarova, E., & Williams, J. M. (2013). Mindfulness online: an evaluation of the feasibility of a web-based mindfulness course for stress, anxiety and depression. *BMJ Open, 3*(11), e003498. doi:10.1136/bmjopen-2013-003498

Kryscio, R. J., Schmitt, F. A., Salazar, J. C., Mendiondo, M. S., & Markesbery, W. R. (2006). Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology, 66*(6), 828-832. doi:10.1212/01.wnl.0000203264.71880.45

Kuhel, D. G., Konaniah, E. S., Basford, J. E., McVey, C., Goodin, C. T., Chatterjee, T. K., . . . Hui, D. Y. (2013). Apolipoprotein E2 accentuates postprandial inflammation and diet-induced obesity to promote hyperinsulinemia in mice. *Diabetes, 62*(2), 382-391. doi:10.2337/db12-0390

Lakhan, S. E., & Schofield, K. L. (2013). Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. *PLoS One, 8*(8), e71834. doi:10.1371/journal.pone.0071834

Larner, A. (2012). Screening utility of the Montreal Cognitive Assessment (MoCA): in place of–or as well as–the MMSE? *International Psychogeriatrics, 24*(03), 391-396.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*(2), 73-81. doi:10.7326/0003-4819-144-2-200601170-00004

Laws, S. M., Clarnette, R. M., Taddei, K., Martins, G., Paton, A., Hallmayer, J., . . . Martins, R. N. (2002). APOE-epsilon4 and APOE -491A polymorphisms in individuals with subjective memory loss. *Mol Psychiatry, 7*(7), 768-775. doi:10.1038/sj.mp.4001083

Lezak, M. D. (1976). *Neuropsychological assessment*. New York: Oxford University Press.

Lezak, M. D. (1983). *Neuropsychological assessment* (2nd ed.). New York: Oxford University Press.

Lippa, S. M. (2018). Performance validity testing in neuropsychology: a clinical guide, critical review, and update on a rapidly evolving literature. *Clin Neuropsychol, 32*(3), 391-421. doi:10.1080/13854046.2017.1406146

Longley, S. L., Broman-Fulks, J. J., Calamari, J. E., Noyes, R., Wade, M., & Orlando, C. M. (2010). A taxometric study of hypochondriasis symptoms. *Behav Ther, 41*(4), 505-514. doi:10.1016/j.beth.2010.02.002

Lovas, D. A., & Barsky, A. J. (2010). Mindfulness-based cognitive therapy for hypochondriasis, or severe health anxiety: a pilot study. *J Anxiety Disord, 24*(8), 931-935. doi:10.1016/j.janxdis.2010.06.019

M Mitrushina, K. B., J Razani, LF D'Elia. (2005). *Handbook of normative data for neuropsychological assessment*: Oxford University Press.

Majdan, A., Sziklas, V., & Jones-Gotman, M. (1996). Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuoperceptual learning. *J Clin Exp Neuropsychol, 18*(3), 416-430. doi:10.1080/01688639608408998

Memel, M., Woolverton, C. B., Bourassa, K., & Glisky, E. L. (2018). Working memory predicts subsequent episodic memory decline during healthy cognitive aging: evidence from a cross-lagged panel design. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 1-20. doi:10.1080/13825585.2018.1521507

Metternich, B., Schmidtke, K., Harter, M., Dykierek, P., & Hull, M. (2010). [Development and evaluation of a group therapy for functional memory and attention disorder]. *Psychother Psychosom Med Psychol, 60*(6), 202-210. doi:10.1055/s-0028-1103281

Metternich, B., Schmidtke, K., & Hull, M. (2009). How are memory complaints in functional memory disorder related to measures of affect, metamemory and cognition? *Journal of Psychosomatic Research, 66*(5), 435-444. doi:10.1016/j.jpsychores.2008.07.005

Miners, S., Ashby, E., Baig, S., Harrison, R., Tayler, H., Speedy, E., . . . Kehoe, P. G. (2009). Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. *Am J Transl Res, 1*(2), 163-177.

Mitchell, A. J., Beaumont, H., Ferguson, D., Yadegarfar, M., & Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand, 130*(6), 439-451. doi:10.1111/acps.12336

Moore, A., & Malinowski, P. (2009). Meditation, mindfulness and cognitive flexibility. *Conscious Cogn, 18*(1), 176-186. doi:10.1016/j.concog.2008.12.008

Moreno-Grau, S., Rodriguez-Gomez, O., Sanabria, A., Perez-Cordon, A., Sanchez-Ruiz, D., Abdelnour, C., . . . group, F. s. (2018). Exploring APOE genotype effects on Alzheimer's disease risk and amyloid beta burden in individuals with subjective cognitive decline: The FundacioACE Healthy Brain Initiative (FACEHBI) study baseline results. *Alzheimers Dement, 14*(5), 634-643. doi:10.1016/j.jalz.2017.10.005

Moreno-Grau, S., & Ruiz, A. (2016). Genome research in pre-dementia stages of Alzheimer's disease. *Expert Rev Mol Med, 18*, e11. doi:10.1017/erm.2016.12

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Wilson, R. S., . . . Schneider, J. (2003). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Archives of neurology, 60*(7), 940-946. doi:DOI 10.1001/archneur.60.7.940

Morris, M. C., Evans, D. A., Tangney, C. C., Bienias, J. L., & Wilson, R. S. (2005). Fish consumption and cognitive decline with age in a large community study. *Archives of neurology, 62*(12), 1849-1853. doi:DOI 10.1001/archneur.62.12.noc50161

Muller-Gerards, D., Weimar, C., Abramowski, J., Tebrugge, S., Jokisch, M., Dragano, N., . . . Heinz Nixdorf Recall Study Investigative, G. (2019). Subjective cognitive decline, APOE epsilon4, and incident mild cognitive impairment in men and women. *Alzheimers Dement (Amst), 11*, 221-230. doi:10.1016/j.dadm.2019.01.007

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53*(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., . . . Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet, 385*(9984), 2255-2263. doi:10.1016/S0140-6736(15)60461-5

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., . . . Kivipelto, M. (2015). *A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial*. Place of publication not identified: Elsevier.

Norton, P. J. (2007). Depression Anxiety and Stress Scales (DASS-21): psychometric analysis across four racial groups. *Anxiety Stress Coping, 20*(3), 253-265. doi:10.1080/10615800701309279

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research, 24*(3), 218-226. doi:10.3275/7800

O'Bryant, S. E., Gavett, B. E., McCaffrey, R. J., O'Jile, J. R., Huerkamp, J. K., Smitherman, T. A., & Humphreys, J. D. (2008). Clinical utility of Trial 1 of the Test of Memory Malingering (TOMM). *Appl Neuropsychol, 15*(2), 113-116. doi:10.1080/09084280802083921

Olatunji, B. O., Etzel, E. N., Tomarken, A. J., Ciesielski, B. G., & Deacon, B. (2011). The effects of safety behaviors on health anxiety: an experimental investigation. *Behav Res Ther, 49*(11), 719-728. doi:10.1016/j.brat.2011.07.008

Ott, A., Slooter, A. J., Hofman, A., van Harskamp, F., Witteman, J. C., Van Broeckhoven, C., . . . Breteler, M. M. (1998). Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet, 351*(9119), 1840-1843. doi:10.1016/s0140-6736(97)07541-7

Ott, B. R., & Owens, N. J. (1998). Complementary and alternative medicines for Alzheimer's disease. *J Geriatr Psychiatry Neurol, 11*(4), 163-173. doi:10.1177/089198879901100401

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., . . . Ballard, C. G. (2010). Putting brain training to the test. *Nature, 465*(7299), 775-778. doi:10.1038/nature09042

Pace, G., Orru, G., Monaro, M., Gnoato, F., Vitaliani, R., Boone, K. B., . . . Sartori, G. (2019). Malingering Detection of Cognitive Impairment With the b Test Is Boosted Using Machine Learning. *Front Psychol, 10*, 1650. doi:10.3389/fpsyg.2019.01650

Pennington, C., Ball, H., & Swirski, M. (2019). Functional Cognitive Disorder: Diagnostic Challenges and Future Directions. *Diagnostics (Basel), 9*(4). doi:10.3390/diagnostics9040131

Pennington, C., Hayre, A., Newson, M., & Coulthard, E. (2015). Functional Cognitive Disorder: A Common Cause of Subjective Cognitive Symptoms. *J Alzheimers Dis, 48 Suppl 1*, S19-24. doi:10.3233/JAD-150182

Pennington, C., Newson, M., Hayre, A., & Coulthard, E. (2015). Functional cognitive disorder: what is it and what to do about it? *Pract Neurol, 15*(6), 436-444. doi:10.1136/practneurol-2015-001127

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., . . . Jack, C. R. (2009). Mild Cognitive Impairment Ten Years Later. *Archives of neurology, 66*(12), 1447-1455. doi:DOI 10.1001/archneurol.2009.266

Petersen, R. C., Waring, S. C., Smith, G. E., Ivnik, R. J., & Kokmen, E. (1997). Mild cognitive impairment: Normal aging or early Alzheimer's disease? *Annals of Neurology, 42*(3), M18-M18.

Pham, E., Crews, L., Ubhi, K., Hansen, L., Adame, A., Cartier, A., . . . Masliah, E. (2010). Progressive accumulation of amyloid-beta oligomers in Alzheimer's disease and in amyloid precursor protein transgenic mice is accompanied by selective alterations in synaptic scaffold proteins. *Febs Journal, 277*(14), 3051-3067. doi:10.1111/j.1742-4658.2010.07719.x

Ponds, R. W., & Jolles, J. (1996). The Abridged Dutch Metamemory in Adulthood (MIA) Questionnaire: structure and effects of age, sex, and education. *Psychol Aging, 11*(2), 324-332.

Power, K., Kirwan, G., & Palmer, M. (2011). A comparison of text and technology based training tools to improve cognitive skills in older adults. *Stud Health Technol Inform, 167*, 98-102.

Prochaska, J. O., Norcross, J. C., & DiClemente, C. C. (1994). *Changing for good : the revolutionary program that explains the six stages of change and teaches you how to free yourself from bad habits*. New York: W. Morrow.

Puskas, L. G., Kitajka, K., Nyakas, C., Barcelo-Coblijn, G., & Farkas, T. (2003). Short-term administration of omega 3 fatty acids from fish oil results in increased transthyretin transcription in old rat hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 100*(4), 1580-1585. doi:10.1073/pnas.0337683100

Raber, J., Huang, Y., & Ashford, J. W. (2004). ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging, 25*(5), 641-650. doi:10.1016/j.neurobiolaging.2003.12.023

Rees, L. M., Tombaugh, T. N., & Boulay, L. (2001). Depression and the Test of Memory Malingering. *Arch Clin Neuropsychol, 16*(5), 501-506.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *J Consult Psychol, 19*(5), 393-394.

Richter, Y., Herzog, Y., Eyal, I., & Cohen, T. (2011). Cognitex supplementation in elderly adults with memory complaints: an uncontrolled open label trial. *J Diet Suppl, 8*(2), 158-168. doi:10.3109/19390211.2011.569514

Ridha, B. H., Barnes, J., Bartlett, J. W., Godbolt, A., Pepple, T., Rossor, M. N., & Fox, N. C. (2006). Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. *Lancet Neurol, 5*(10), 828-834. doi:10.1016/S1474-4422(06)70550-6

Riedel-Heller, S. G., Matschinger, H., Schork, A., & Angermeyer, M. C. (1999). Do memory complaints indicate the presence of cognitive impairment? Results of a field study. *European Archives of Psychiatry and Clinical Neuroscience, 249*(4), 197-204. doi:DOI 10.1007/s004060050087

Risacher, S. L., Kim, S., Nho, K., Foroud, T., Shen, L., Petersen, R. C., . . . Alzheimer's Disease Neuroimaging, I. (2015). APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern. *Alzheimers Dement, 11*(12), 1417-1429. doi:10.1016/j.jalz.2015.03.003

Ritchie, K., Carriere, I., de Mendonca, A., Portet, F., Dartigues, J. F., Rouaud, O., . . . Ancelin, M. L. (2007). The neuroprotective effects of caffeine - A prospective population study (the Three City Study). *Neurology, 69*(6), 536-545. doi:DOI 10.1212/01.wnl.0000266670.35219.0c

Rovio, S., Kareholt, I., Helkala, E. L., Viitanen, M., Winblad, B., Tuomilehto, J., . . . Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol, 4*(11), 705-711. doi:10.1016/S1474-4422(05)70198-8

Ruitenberg, A., van Swieten, J. C., Witteman, J. C., Mehta, K. M., van Duijn, C. M., Hofman, A., & Breteler, M. M. (2002). Alcohol consumption and risk of dementia: the Rotterdam Study. *Lancet, 359*(9303), 281-286. doi:10.1016/S0140-6736(02)07493-7

Sachdev, P. S., Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N., . . . Sydney Memory, A. S. T. (2013). Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. *PLoS One, 8*(3), e59649. doi:10.1371/journal.pone.0059649

Sachdev, P. S., Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N., . . . Team, S. M. A. S. (2013). Factors Predicting Reversion from Mild Cognitive Impairment to Normal Cognitive Functioning: A Population-Based Study. *PLoS One, 8*(3). doi:ARTN e59649

10.1371/journal.pone.0059649

Salkovskis, P. M., Rimes, K. A., Warwick, H. M. C., & Clark, D. M. (2002). The Health Anxiety Inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychological Medicine, 32*(5), 843-853. doi:10.1017/S0033291702005822

Salkovskis, P. M., & Salkovskis, P. M. (1996). *Trends in cognitive and behavioural therapies*. Chichester ; New York: Wiley.

Saunders, P. A., Copeland, J. R., Dewey, M. E., Davidson, I. A., McWilliam, C., Sharma, V., & Sullivan, C. (1991). Heavy drinking as a risk factor for depression and dementia in elderly men. Findings from the Liverpool longitudinal community study. *Br J Psychiatry, 159*, 213-216. doi:10.1192/bjp.159.2.213

Scarmeas, N., Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology, 57*(12), 2236-2242. doi:10.1212/wnl.57.12.2236

Scarmeas, N., Stern, Y., Tang, M. X., Mayeux, R., & Luchsinger, J. A. (2006). Mediterranean diet (MeDi) and risk of Alzheimer's disease (AD). *Neurology, 66*(5), 309-309.

Schmidtke, K. (1995). [Functional memory disorders. A study of 25 patients]. *Nervenarzt, 66*(5), 338-346.

Schmidtke, K., & Metternich, B. (2009). Validation of two inventories for the diagnosis and monitoring of functional memory disorder. *J Psychosom Res, 67*(3), 245-251. doi:10.1016/j.jpsychores.2009.04.005

Shapiro, S. L., Schwartz, G. E., & Bonner, G. (1998). Effects of mindfulness-based stress reduction on medical and premedical students. *J Behav Med, 21*(6), 581-599.

Sharpe, M., Peveler, R., & Mayou, R. (1992). The psychological treatment of patients with functional somatic symptoms: a practical guide. *J Psychosom Res, 36*(6), 515-529.

Shukitt-Hale, B. (2012). Blueberries and Neuronal Aging. *Gerontology, 58*(6), 518-523. doi:10.1159/000341101

Skoog, I., Waern, M., Duberstein, P., Blennow, K., Zetterberg, H., Borjesson-Hanson, A., . . . Kern, S. (2015). A 9-year prospective population-based study on the association between the APOE*E4 allele and late-life depression in Sweden. *Biol Psychiatry, 78*(10), 730-736. doi:10.1016/j.biopsych.2015.01.006

Slavin, M. J., Brodaty, H., Kochan, N. A., Crawford, J. D., Trollor, J. N., Draper, B., & Sachdev, P. S. (2010). Prevalence and Predictors of "Subjective Cognitive Complaints" in the Sydney Memory and Ageing Study. *American Journal of Geriatric Psychiatry, 18*(8), 701-710. doi:10.1097/JGP.0b013e3181df49fb

Small, G. W., Chen, S. T., Komo, S., Ercoli, L., Bookheimer, S., Miller, K., . . . Pericak-Vance, M. A. (1999). Memory self-appraisal in middle-aged and older adults with the apolipoprotein E-4 allele. *Am J Psychiatry, 156*(7), 1035-1038. doi:10.1176/ajp.156.7.1035

Small, S. A., Perera, G. M., DeLaPaz, R., Mayeux, R., & Stern, Y. (1999). Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Ann Neurol, 45*(4), 466-472.

Smart, C. M., Segalowitz, S. J., Mulligan, B. P., & MacDonald, S. W. S. (2014). Attention capacity and self-report of subjective cognitive decline: A P3 ERP study. *Biological Psychology, 103*, 144-151. doi:10.1016/j.biopsycho.2014.08.016

Solfrizzi, V., Panza, F., & Capurso, A. (2003). The role of diet in cognitive decline. *J Neural Transm (Vienna), 110*(1), 95-110. doi:10.1007/s00702-002-0766-8

Stella, F., Radanovic, M., Balthazar, M. L., Canineu, P. R., de Souza, L. C., & Forlenza, O. V. (2014). Neuropsychiatric symptoms in the prodromal stages of dementia. *Curr Opin Psychiatry, 27*(3), 230-235. doi:10.1097/YCO.0000000000000050

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004

Stewart, R. (2012). Subjective cognitive impairment. *Current Opinion in Psychiatry, 25*(6), 445-450. doi:10.1097/YCO.0b013e3283586fd8

Striepens, N., Scheef, L., Wind, A., Meiberth, D., Popp, J., Spottke, A., . . . Jessen, F. (2011). Interaction effects of subjective memory impairment and ApoE4 genotype on episodic memory and hippocampal volume. *Psychol Med, 41*(9), 1997-2006. doi:10.1017/S0033291711000067

Suhr, J. A., & Gunstad, J. (2005). Further exploration of the effect of "diagnosis threat" on cognitive performance in individuals with mild head injury. *J Int Neuropsychol Soc, 11*(1), 23-29. doi:10.1017/S1355617705050010

Sullivan, K., & Bowden, S. C. (1997). Which tests do neuropsychologists use? *Journal of Clinical Psychology, 53*(7), 657-661. doi:10.1002/(sici)1097-4679(199711)53:7<657::aid-jclp3>3.0.co;2-f

Sydenham, E., Dangour, A. D., & Lim, W. S. (2012). Omega 3 fatty acid for the prevention of cognitive decline and dementia. *Cochrane Database of Systematic Reviews*(6). doi:ARTN CD005379

10.1002/14651858.CD005379.pub3

Tales, A., Jessen, F., Butler, C., Wilcock, G., Phillips, J., & Bayer, T. (2015a). Subjective Cognitive Decline. *J Alzheimers Dis, 48 Suppl 1*, S1-3. doi:10.3233/JAD-150719

Tales, A., Jessen, F., Butler, C., Wilcock, G., Phillips, J., & Bayer, T. (2015b). Subjective Cognitive Decline Preface. *Journal of Alzheimers Disease, 48*, S1-S3. doi:10.3233/Jad-150719

Tanaka, H., & Shirakawa, S. (2004). Sleep health, lifestyle and mental health in the Japanese elderly: ensuring sleep to promote a healthy brain and mind. *J Psychosom Res, 56*(5), 465-477. doi:10.1016/j.jpsychores.2004.03.002

Teasdale, J. D., Segal, Z. V., Williams, J. M., Ridgeway, V. A., Soulsby, J. M., & Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol, 68*(4), 615-623.

Thiel, C., Vogt, L., Tesky, V. A., Meroth, L., Jakob, M., Sahlender, S., . . . Banzer, W. (2012). Cognitive intervention response is related to habitual physical activity in older adults. *Aging Clinical and Experimental Research, 24*(1), 47-55. doi:10.3275/7569

Tierney, M. C., Szalai, J. P., Snow, W. G., Fisher, R. H., Nores, A., Nadon, G., . . . St George-Hyslop, P. H. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology, 46*(3), 661-665. doi:10.1212/wnl.46.3.661

Tombaugh, T. N. (1997). The test of memory malingering (TOMM): Normative data from cognitively intact and cognitively impaired individuals. *Psychological Assessment, 9*(3), 260-268. doi:Doi 10.1037/1040-3590.9.3.260

Tsoi, K. K. F., Chan, J. Y. C., Hirai, H. W., Wong, A., Mok, V. C. T., Lam, L. C. W., . . . Wong, S. Y. S. (2017). Recall Tests Are Effective to Detect Mild Cognitive Impairment: A Systematic Review and Meta-analysis of 108 Diagnostic Studies. *J Am Med Dir Assoc, 18*(9), 807 e817-807 e829. doi:10.1016/j.jamda.2017.05.016

Uauy, R., & Dangour, A. D. (2006). Nutrition in brain development and aging: role of essential fatty acids. *Nutr Rev, 64*(5 Pt 2), S24-33; discussion S72-91. doi:10.1301/nr.2006.may.s24-s33

Valech, N., Mollica, M. A., Olives, J., Tort, A., Fortea, J., Lleo, A., . . . Rami, L. (2015). Informants' Perception of Subjective Cognitive Decline Helps to Discriminate Preclinical Alzheimer's Disease from Normal Aging. *J Alzheimers Dis, 48 Suppl 1*, S87-98. doi:10.3233/JAD-150117

Valenzuela, M., & Sachdev, P. (2006). Complex mental activity and risk for dementia. *Acta Neuropsychiatr, 18*(6), 272. doi:10.1017/S0924270800030842

van Gelder, B. M., Buijsse, B., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2007). Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. *Eur J Clin Nutr, 61*(2), 226-232. doi:10.1038/sj.ejcn.1602495

Verfaillie, S. C. J., Timmers, T., Slot, R. E. R., van der Weijden, C. W. J., Wesselman, L. M. P., Prins, N. D., . . . van der Flier, W. M. (2019). Amyloid-beta Load Is Related to Worries, but Not to Severity of Cognitive Complaints in Individuals With Subjective Cognitive Decline: The SCIENCe Project. *Front Aging Neurosci, 11*, 7. doi:10.3389/fnagi.2019.00007

Verghese, P. B., Castellano, J. M., & Holtzman, D. M. (2011). Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol, 10*(3), 241-252. doi:10.1016/S1474-4422(10)70325-2

Verhaeghen, P., & Basak, C. (2005). Ageing and switching of the focus of attention in working memory: results from a modified N-back task. *Q J Exp Psychol A, 58*(1), 134-154. doi:10.1080/02724980443000241

Verlinden, V. J. A., van der Geest, J. N., de Bruijn, R., Hofman, A., Koudstaal, P. J., & Ikram, M. A. (2016). Trajectories of decline in cognition and daily functioning in preclinical dementia. *Alzheimers Dement, 12*(2), 144-153. doi:10.1016/j.jalz.2015.08.001

Wang, P. N., Lirng, J. F., Lin, K. N., Chang, F. C., & Liu, H. C. (2006). Prediction of Alzheimer's disease in mild cognitive impairment: a prospective study in Taiwan. *Neurobiol Aging, 27*(12), 1797-1806. doi:10.1016/j.neurobiolaging.2005.10.002

Ward, A., Crean, S., Mercaldi, C. J., Collins, J. M., Boyd, D., Cook, M. N., & Arrighi, H. M. (2012). Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology, 38*(1), 1-17. doi:10.1159/000334607

Warwick, H. M., & Salkovskis, P. M. (1990). Hypochondriasis. *Behaviour Research and Therapy, 28*(2), 105-117. doi:10.1016/0005-7967(90)90023-c

Weiner, M. F., Bruhn, M., Svetlik, D., Tintner, R., & Hom, J. (1991). Experiences with depression in a dementia clinic. *J Clin Psychiatry, 52*(5), 234-238.

Willett, W. C., Sacks, F., Trichopoulou, A., Drescher, G., Ferroluzzi, A., Helsing, E., & Trichopoulos, D. (1995). Mediterranean Diet Pyramid - a Cultural Model for Healthy Eating. *American Journal of Clinical Nutrition, 61*(6), 1402s-1406s. doi:DOI 10.1093/ajcn/61.6.1402S

Williams, M. J., McManus, F., Muse, K., & Williams, J. M. (2011). Mindfulness-based cognitive therapy for severe health anxiety (hypochondriasis): an interpretative phenomenological analysis of patients' experiences. *Br J Clin Psychol, 50*(4), 379-397. doi:10.1111/j.2044-8260.2010.02000.x

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *Jama, 287*(6), 742-748. doi:10.1001/jama.287.6.742

Ybarra, O., Burnstein, E., Winkielman, P., Keller, M. C., Manis, M., Chan, E., & Rodriguez, J. (2008). Mental exercising through simple socializing: social interaction promotes general cognitive functioning. *Pers Soc Psychol Bull, 34*(2), 248-259. doi:10.1177/0146167207310454

Zeidan, F., Johnson, S. K., Diamond, B. J., David, Z., & Goolkasian, P. (2010). Mindfulness meditation improves cognition: evidence of brief mental training. *Conscious Cogn, 19*(2), 597-605. doi:10.1016/j.concog.2010.03.014

Zeljko, H. M., Skaric-Juric, T., Narancic, N. S., Tomas, Z., Baresic, A., Salihovic, M. P., . . . Janicijevic, B. (2011). E2 allele of the apolipoprotein E gene polymorphism is predictive for obesity status in Roma minority population of Croatia. *Lipids Health Dis, 10*, 9. doi:10.1186/1476-511X-10-9

Zunzunegui, M. V., Alvarado, B. E., Del Ser, T., & Otero, A. (2003). Social networks, social integration, and social engagement determine cognitive decline in community-dwelling Spanish older adults. *J Gerontol B Psychol Sci Soc Sci, 58*(2), S93-S100. doi:10.1093/geronb/58.2.s93

Appendix 1

DECODE study Participant Information sheet

Brain Centre
Elgar House
Southmead Hospital
Westbury on Trym
Bristol
BS10 5NB
Tel: 0117 414 8182
Version 2: 02/01/2017

DECODE - Development and Evaluation of Interventions in People with Subjective Cognitive Decline

Participant Information Sheet

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to your friends and family about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear.

Part 1

What is the purpose of this study?

The aim of this study is to explore whether mindfulness or lifestyle factors courses for people with Subjective Cognitive Decline have an effect on their memory and thinking and well-being.
Subjective Cognitive Decline describes individuals who are experiencing decline in their thinking abilities, more than just normal ageing.

Why have I been invited?

You are aged over 45 and are concerned about your memory or thinking, but do not have a diagnosis of dementia. You may either have responded to our advertising, been written to or contacted by your GP or Memory Clinic.

Do I have to take part?
No. It is entirely up to you, taking part is voluntary and you may decline to take part or leave the study at any time without having to give a reason. If you do decide to take part you should read this information sheet carefully and will be asked to sign the consent form at the screening clinic appointment to show you have agreed to take part. You will get a copy of this consent form.

Reasons you may not be suitable to take part in the study
This study involves participation in one of 3 groups: mindfulness course, lifestyle factors course or control. Since we don't know yet in which group you will be assigned, we aim to make sure that all participants are eligible for all interventions.

You may not be suitable to take part in the study if it is unsafe for you to take part in a physical activity regime. You will be given a questionnaire to check this over the phone, before your first visit and you may be asked to double-check with your doctor to make sure is safe for you to do a 15 minutes brisk walk, 3 times per week. During this call we will also ask you some background questions to make sure you are suitable for the study.

What will happen to me if I take part?
If you are suitable for the study, you will be invited to attend a screening appointment at the Brain Centre, Southmead Hospital. You will be given an opportunity to discuss the study, ask any questions and if still happy to take part, you will sign the consent form prior to undertaking any study assessments.

The study will include:

- A baseline assessment of approximately 1 ½ hours: Brief memory tests and questionnaires assessing daily living/mood/general health.
- An optional blood test (for examining any relationship between cognitive scores and a specific apolipoprotein, provided you do not already know your ApoE genotype). We expect that people with the ApoE4 genotype will respond differently to the interventions. We would also like to assess the biochemical profile as this can be influenced by lifestyle factors. In particular, we expect to find a relationship between the blood biochemical profiles, such as fat and protein metabolism and cognitive function, which impact how people respond to mindfulness. If you do not wish to have a blood test you may continue to participate in the rest of the study.
- Getting assigned into one of three groups:
    1. Meditation (4-week online course done at home). The course includes 10 online sessions lasting 30 minutes each.
    2. Lifestyle factors (4-week online course done at home).The course includes 4 video presentations with total duration of approximately 1 hour. If you don't have access to a computer, you can use one of the computers at the Brain Centre for the above online courses.
    3. Control group (no intervention at the time of testing but, you will be offered the lifestyle intervention after the end of the study).
- Repeating the baseline assessment right after completing the intervention and once again, after a period of 6 months.
- Completing daily short diaries (regarding hours of sleep, eating habits, exercise, etc.) for one week before starting the course, one week right after completing it and finally, for one week before repeating the final assessment after 6 months.

- Participants in the lifestyle factors course will also be asked to complete a physical activity sheet for the duration of the course (4 weeks).

Your results are confidential and they will not be disclosed to you, unless they raise a concern.

If any cause for concern is raised by your test results at any point (baseline assessment, assessment after completing the intervention, or 6 months follow-up assessment) we will provide written feedback, discuss this with you and if appropriate, inform your GP of our findings so he/she can further assess or refer you as required. In this case you will no longer be eligible for participation in the study.

Expenses and payments
You will be reimbursed for travel and any other reasonable expenses incurred as a result of taking part in the study.

What will I have to do?
Complete the tests, questionnaires and diaries, as well as one of the interventions as described above under the section "What will happen to me if I take part?"

What are the possible disadvantages and risks of taking part?
Due to the sensitive nature of the questionnaires there is a potential for upset during the assessment sessions. In the unlikely event that you find the tests upsetting you can discuss this with the examiner at the time (Chara Triantafyllou or Alice Storey) and are free to withdraw from the study. Significant concerns or distress will be passed on to Dr Margaret Newson who is a Clinical Neuropsychologist.

Please keep in mind that if you find any of the questionnaires or study procedures difficult, distressing or boring, you are free to withdraw from the study and/or refuse to complete any of the tests, or parts of tests, at any time.

Risks Associated with Blood samples
We invite you to provide an optional blood sample. The physical risks of giving this blood sample are the same as any blood sample taken from a vein. You may experience minor bruising or irritation.

What are the possible benefits of taking part?
Through this study you will have the chance to participate in courses that might improve your quality of life. Even if you get assigned to the control group, you will be offered the lifestyle factors course at the end of the study.

What happens when the research study stops?
Once we collect all of our data, we will analyse it and write up the results for the main researcher's PhD and for publications in scientific journals.

Who is going to be at the assessment sessions?
There will be one examiner in the assessment sessions. This will be either the main researcher (Chara Triantafyllou) or the placement student (Alice Storey) assisting with the study. The blood samples will be collected by the main researcher (Chara Triantafyllou).

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

This completes Part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the study?
You can choose to withdraw from the study at any time without giving a reason. We will keep the results already collected unless you request us not to.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (see contact details on the last page).

If you have any questions regarding the group you have been assigned to, please contact Dr Margaret Newson.

If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be found in the Complaints procedure leaflet for North Bristol NHS Trust, or http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/NHScomplaints.aspx

Harm
We do not expect you would come to any harm as a result of taking part in the study. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against University of Bristol, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?
Yes. We will follow ethical and legal practice and all information collected about you during the course of the research will be kept strictly confidential. We will give you a unique identifiable number against which we will store all your data. Study data are stored at the Brain Centre, in locked cabinets located at the researchers' offices. No one, except the named investigators, would have access to your study data. No personally identifying details will appear in our published results or in any direct quotations.

What will happen to the results of the research study?
The results of the study may be presented at conferences and published in medical or scientific journals. If you would like, we can inform you of where you can obtain a copy of the published results (please indicate your interest in the Consent form). Only the group findings will be available and it will not be possible to identify your individual results.

The information collected during this study may also be added to research databases and used in the future by the ReMemBr group with your permission, in order to:

- Develop a better understanding of memory disorders and study alternative interventions.
- Improve the efficiency and the design of future studies.

What will happen to my samples?
If you consent to a blood test, your anonymised sample will be transferred to our collaborators for identification of ApoE genotype. Given the scope of this study genetic counselling would be beyond our remit and hence these results will not be disclosed to you. If you also consent to storage, we will store your sample for future research purposes.

Who is organising and funding the research?
Dr Elizabeth Coulthard and colleagues, Dr Margaret Newson and PhD student Chara Triantafyllou are organising the study. University of Bristol is the sponsor and funding has been awarded by BRACE charity.

Who has reviewed the study?
(TO BE CONFIRMED)
All research in the NHS is looked at by an independent group of people, called the Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the XX NHS Research Ethics Committee.

Thank you for considering taking part in this study.

Contacts for further Information:

Chara Triantafyllou
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University of Bristol
ReMemBr group (North Bristol NHS Trust)
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Dr Margaret Newson
Senior Clinical Neuropsychologist
North Bristol NHS Trust

ReMemBr Group

Appendix 2

The Lifestyle Factors Intervention

In order to access the online course 4 Week Change Challenge please visit the web site www.lifestylefactorsinterventions.com *and insert:*

Username: Visitor
Password: Lifestylecourse@visitor_01

Appendix 3

Screening questionnaire

Date:.....

1. Age:
2. Gender:
3. Any diagnosis of dementia:
4. Any diagnosis of cognitive impairment:
5. Other neurological condition (e.g., Parkinson's disease, Multiple sclerosis, brain injury or infection, etc.):
6. Other psychiatric condition:
7. Do you know your ApoE genotype? Yes / No

Appendix 4

Background Information Questionnaire

Pre-screening question

Are you concerned or worried that you are experiencing significant decline in your thinking abilities, more than just normal ageing?

Part 1. Demographics

1. Gender:
2. Area of residence: urban/suburban/rural
3. Who do you live with:
4. Smoking: Current/EX/Never
   How much?
5. Alcohol use (units/week):
6. Physical activity level: Yes/No
   What kind?
   How much?
7. Height:
8. Weight:
9. Body Mass index:
10. Do you practice formal meditation: Yes/No
    How often?

Part 2. Health concerns behaviour

1. Have you sought help about your memory prior to coming here? Yes/No
2. How many times have you seen your GP in the past year?

Part 3. Past medical history

8. Raised cholesterol: Yes/No/Don't know
9. Diabetes: Yes/No/Don't know
10. Stroke: Yes/No/Don't know
11. Transient Ischemic attack (TIA): Yes/No/Don't know
12. Heart disease: Yes/No/Don't know and what kind (e.g. Atrial fibrillation)?
13. Other neurological condition (e.g., Parkinson's disease, Multiple sclerosis, brain injury or infection, etc.): Yes/No/Don't know
14. Family history of Alzheimer's disease or other form of dementia: Yes/No/Don't know
15. Past history depression: Yes/No/Don't know
16. Past history anxiety: Yes/No/Don't know
17. Other psychiatric condition: Yes/No/Don't know

18. Any other medical condition we have not asked about (e.g., cancer, long-term illness)?
19. Medications (aspirin, antihypertensives, heart meds): Yes/No
    If yes, please list medication names and doses:

Appendix 5

Diary

Diary

This diary is for keeping track of different lifestyle factors each day.

Please answer all of the questions as honestly and accurately as possible.

Participant ID: **Date:**

Week (Please circle): Baseline / 4 weeks / 6 months

Day (Please circle): 1, 2, 3, 4, 5, 6, 7

Food today

1. Portions of fish (e.g. fresh fish, fish cakes, fish sticks): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
2. Portions of green leafy vegetables (e.g. spinach, lettuce): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
3. Portions of other vegetables: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
4. Portions of fruits: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
5. Number of snacks (e.g. cakes, pastries, crisps): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
6. Portions of nuts (e.g. almonds, walnuts, peanuts): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
7. Portions of grains (e.g. oats, rice): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
8. Portions of pulses (e.g. lentils, beans): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
9. Portions of fatty red meat (e.g. bacon, sausage, ham): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
10. Portions of lean meat/poultry (e.g. lean beef/pork, chicken): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
11. Portions of dairy products: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
12. Olive oil: Yes / No

<u>Portions explained:</u>

Vegetables: 1 portion= 2 broccoli spears or 4 heaped tablespoons of cooked spinach/kale, or 1 dessert bowl of salad, etc.

Fruits: 1 portion= 1 apple, 1 banana, 1 orange etc. or 2 plums, 2 kiwis, etc. or ½ a grapefruit, ½ avocado etc. or 2 handfuls of blueberries, etc.

Nuts: 1 portion= ¼ cup of walnuts, almond, etc.

Grains: 1 portion= 1 slice of bread, or ½ cup cooked rice/pasta/noodles, or ½ cup oatmeal

Pulses: 1 portion= 3 heaped tablespoons of baked beans/chickpeas, etc.

Fish/Meat/Lean meat/Poultry: 100g cooked fish fillet, or 65g cooked red meat (such as beef, lamb, veal or pork), or 1 sausage (50g), or 80g cooked poultry (such as chicken or turkey)

Dairy: 1 portion= 1 cup of milk, or 40g of hard cheese (such as cheddar), or ½ ricotta cheese, or ¾ cup yoghurt

Beverages today

11. Number of cups of coffee: ……

12. Number of cups of tea: ……

13. Number of other drinks with caffeine (e.g. coke, pepsi, red bull):

……..

Alcohol & Cigarettes today

14. Number of cigarettes smoked:

…….....

15. Number of units* of alcohol consumed: .....

16. Type of alcohol consumed (beer, wine, spirits): .....
If you are not sure, just describe how much alcohol you had:……

*units: 1 pint of lower-strength beer/cider= 2 units, 1 pint of higher-strength beer/cider= 3 units, 1 bottle of beer/cider= 1.7 units, 1 can of beer/cider= 2 units, 1 small glass of wine= 1.5 units, 1 standard glass of wine= 2.1 units, 1 large glass of wine= 3 units, about ½ pint, small glass of wine, 1 single shot of spirit= 1 unit

Exercise today

17a. Brisk walking you did today (time in min):

.....

17b. Any other exercise (type and time in min):

…….....

Mindfulness Meditation today

18. Meditation (minutes):

Sleep last night

19. How many hours (you can record fractions of hours, like 6 ¼):

Mentally stimulating activities today

20. How many mentally stimulating activities (e.g. reading, doing puzzles, playing a musical instrument): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10+

- What kind of activity/activities?

  ……

  ……

- Total time of activity/activities?

  ……

Social interaction today

21. How many face-to-face contacts with a friend, colleague, acquaintance or relative who does not live with you (e.g. interactions with a social group, volunteering or meeting with a friend): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10+

- Type of contacts:.....
- Total time of face-to-face contacts with a friend or a relative (minutes or hours):……..

22. How many <u>other</u> contacts with a friend, colleague, acquaintance or relative that was not face-to-face (e.g. telephone, email, chatrooms, etc.) today: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10+

- Type of contacts:.....
- Total time of <u>other</u> contacts with a friend or relative today (minutes or hours):.....

That is the end of the diary questionnaire.

Please feel free to write any additional comments in the section below:

……
……
……

Appendix 6

Readiness to Change Questionnaire

1. Exercise
   a. Do you exercise? Yes/No
   b. In the past year, have you made a change to your **level of exercise** (circle the answer)?

      A. More than 6 months ago
      B. Less than 6 months ago
      C. I am intending to change in the next month
      D. I am intending to change in the next 6 months
      E. I am not intending to change

2. Meditation
   a. Do you meditate? Yes/No
   b. In the past year, have you made a change to your **meditation practice** (circle the answer)?

      A. More than 6 months ago
      B. Less than 6 months ago
      C. I am intending to change in the next month
      D. I am intending to change in the next 6 months
      E. I am not intending to change